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VISCERAL LARVA MIGRANS*

Report of the Syndrome in Three Siblings

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BOSTON

VISCERAL larva migrans, a syndrome with a wide variety of manifestations, is frequently not recognized. It has implications of importance to all physicians. Beaver et al.[1] and Smith and Beaver[2] have shown that this syndrome is caused by the ingestion of embryonated ova of dog or cat roundworms (*Toxocara canis* or *Toxocara mystax*). Similar syndromes are caused by other parasites.[3,4] The most consistent finding in visceral larva migrans has been a leukocytosis with marked esosinophilia. White-cell counts usually range from 12,000 to 100,000, with eosinophils making up 15 to 80 per cent of the total. Eosinophilia may persist for several months to several years and has been used as a crude indicator of the activity of the disease. Hepatomegaly has been said to be constant,[5] but current experience at the Children's Hospital indicates that this need not always be so. Zuelzer and Apt[6] likewise described 2 patients who probably had visceral larva migrans but did not have enlarged livers. Splenomegaly is common. Pulmonary infiltration, leading to respiratory distress, usually with wheezing, may be the most prominent manifestation and may even result in death. Rashes of various kinds are also often seen.

FIGURE 1. *Photographs of N.S., Showing the Degree of Hepatosplenomegaly and the Extent of the Rash on April 14, 1955.*

A B

FIGURE 2. *Rash on the Right Thigh of N.S.*
Note the spread and change in character of the lesions between the times of the two photographs (taken on December 3, 1954, and April 14, 1955). There was no response to 1 per cent hydrocortisone ointment applied four times daily. Subsequently, the lesions cleared completely and spontaneously.

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References have been made to the presence of larvae (probably toxocara but not definitely proved to be) in the brain associated with convulsions,[5,7] in the eyes as a probably etiologic factor in "pseudotumor," choroiditis and other disorders,[5,8] and in other organs in which they may be of less danger to the patient.

A helpful laboratory aid has been the detection of hyperglobulinemia. In the cases reported, this is chiefly due to an increase in gamma globulins. It is also of assistance in diagnosis to find fertile toxocara ova in the soil or basement dust of the patient's home. This may be sampled at any time since the eggs have been known to remain intact and viable in soil for several years. Freshly contaminated soil, or a recently passed stool from the family dog or cat, however, provides the best opportunity to identify ova. Immunologic tests, as pointed out below, are now

FIGURE 3. *Photomicrographs of a Skin Biopsy in Case 1, Taken at the Time of the Picture on the Left in Figure 2 (X120), Showing Inflammatory Reaction in the Dermis (Chiefly Histiocytes and Eosinophils).*

showing utility as rough screening procedures and may eventually provide an accurate method of definitive diagnosis. Skin tests similarly are under investigation by Dr. R. C. Jung, of Tulane University, and may become valuable aids in the recognition of infection with toxocara. Liver biopsy does not seem warranted in most cases since it is rarely necessary for diagnosis of the syndrome, seldom yields a definitive answer (larvae as such are infrequently found) and would not influence the therapeutic approach.

Visceral larva migrans is usually seen in children between one and four years of age since it is often associated with pica, which occurs chiefly in this age group and results in the ingestion of soil containing toxocara ova. It may occur at other ages, however, even in persons who have no abnormal craving for dirt. For example, ova may be introduced into the intestinal tract when hands are soiled by dirt that has been contaminated with feces from infected animals. It has been shown that as few as 200 total ova, which may be present in a very small volume of ingested material, will produce a mild form of the

FIGURE 4. *Further Magnification (X740) of the Area Indicated in Figure 3, Showing the Fibrinoid Change in Collagen Fibers Seen in the Perivascular Areas.*

disease manifested by marked eosinophilia.[2] It is also well to note that visceral larva migrans is sometimes encountered concurrently with lead poisoning, both being a result of pica. This should immediately come to mind when one sees atypical features such as eosinophilia in patients who have plumbism. Toxocara infection in dogs is relatively common,* and visceral larva migrans in childhood is being recognized with increasing frequency.[9-11]†

*A survey of recent stool examinations at the Angell Memorial Animal Hospital, Boston, revealed that 20 per cent of 992 fecal specimens showed toxocara ova. These ova were most frequent in very young dogs, being considerably less common in adult dogs.

†Eight newly diagnosed cases were observed during a recent seven-month period at the Children's Hospital.

This paper describes the investigations made in a family of 4 children, 3 of whom had clinical manifestations thought to represent visceral larva migrans. Certain features found in these patients but not emphasized in the recent literature are also pointed out, among them being the microscopical appearance of the skin lesions, unusual eosinophils and hypergammaglobulinemia.

Case Reports

Case 1. N.S., a 3-year-old girl, was admitted to the Children's Hospital on December 2, 1954, because of hepatosplenomegaly and a skin rash (Fig. 1) and recurrent pneumonitis. She had been in good health until 6 months previously, when an erythematous urticarial rash was observed on the abdomen and extremities. Four months later the rash became papular and pruritic, and after a few weeks the patient was admitted to another hospital because of respiratory embarrassment, with cyanosis, wheezing and dyspnea of such a degree as to cause concern that she might not survive. The temperature was 101.8°F., and she had marked respiratory distress, with bilateral diffuse pneumonitis, hepatomegaly and an erythematous papular rash. The white-cell count was 21,000, with 8 per cent eosinophils. Oxygen was administered in a tent, and tetracycline, 375 mg., was given daily for 7 days. The first improvement was seen within 18 hours, after which all symptoms gradually subsided so that she was asymptomatic 1 week later when discharged home. Hepatomegaly, however, continued during the ensuing 4½-week interval of apparent good health. Then, 4 days before admission to the Children's Medical Center she had a recurrence of fever, dyspnea and wheezing similar to that noted during the 1st attack. She was readmitted to the other hospital and was given oxygen and mist combined with tetracycline, 250 mg. every 6 hours. The next morning she was almost moribund, responding only slightly to stimuli, and ACTH, 10 mg. intramuscularly every 6 hours, was started. Thereafter there was gradual improvement until, at the end of 4 days, she was considered well enough for transfer to the Children's Hospital.

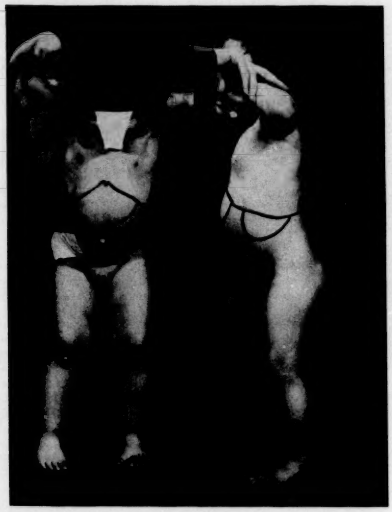

Figure 5. *Photographs of C.S., Showing Hepatosplenomegaly and Prominent Abdomen on February 23, 1955.*

The past history revealed infantile eczema from 2 to 9 months of age and ingestion of raw milk for a 1-year period from the age of 10 months to 22 months. A maternal grandmother has asthma, and a paternal grandfather hay fever. There had been frequent dirt eating, and both a dog and a cat had been in the household for more than 1 year.

Physical examination revealed a well developed and well nourished, responsive child with apparently normal mentality. She had an erythematous papular rash over both wrists and ankles and the right thigh (Fig. 1 and 2), and biopsy of the skin showed an inflammatory reaction in the dermis (Fig. 3), with fibrinoid changes in collagen fibers in the perivascular areas (Fig. 4). There were diffuse inspiratory sibilant rales and mild expiratory wheezes over both lungs. These findings were not accompanied by respiratory distress, cyanosis or digital clubbing. The liver was palpated as a smooth, firm, nontender mass 4 cm. below the right costal border, and the spleen 2 cm. below the left costal margin. There were no abnormal findings in the remainder of the physical examination.

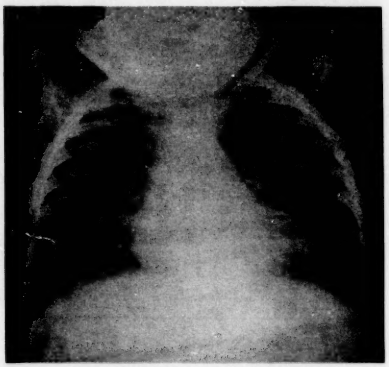

Figure 6. *X-ray Films of the Chest in Case 2. Note the increased density in perihilar regions, with small, scattered areas of focal infiltration, most prominent in the right-lung base.*

Laboratory data are summarized in Table 1, which lists negative as well as positive findings, pointing out some of the diagnostic possibilities and problems for investigation that can arise in such cases. The striking findings included a white-cell count ranging from 20,800 on admission to 8350 on discharge, with eosinophils on repeated counts making up 18 to 67 per cent of the total. The sedimentation rate was normal; there was hypergammaglobulinemia, and liver-function tests were positive. X-ray examination of the chest revealed a definite but nonspecific increase in perihilar markings, with focal areas of inflammatory reaction.

The 9-day course in the hospital was characterized by a gradual disappearance in the pulmonary findings on auscultation, clearing of the lung fields on x-ray study, a moderate decrease in the size of the liver and spleen and a decrease of the leukocytosis, but persistence of eosinophilia and skin rash. While in the hospital the patient was given oxytetracycline, 125 mg. every 6 hours, and syrup of Nethaprin,* ½ teaspoon (2.5 ml.) every 6 hours. No therapy was

*Trade name for a product available from the William S. Merrell Company, Cincinnati, Ohio, and containing the following ingredients in each teaspoonful: methylethylamino-phenylpropanol hydrochloride, 25 mg.; theophylline aminoisobutanol, 60 mg.; and doxylamine succinate, 6 mg.

prescribed on discharge. Simple instructions were given to help overcome the pica, and a suggestion was made that the dog and cat should be removed from the household after appropriate studies. Both animals actually were disposed of, however, before stool samples were obtained for examination. Because of the distance from the Children's Hospital and other difficulties, attempts to find toxocara ova in the soil were limited to the study of a single specimen as indicated in Table 1. On January 27, 1955, the patient had another serious episode of respiratory distress necessitating a 3d admission to the other hospital. She was given tetracycline, 125 mg. every 6 hours, and improvement began 24 to 36 hours later. She has been symptom free since this episode except for a stubborn skin rash, which, however, was not present at her last visit. Hepatosplenomegaly and eosinophilia remained 6 months after the last admission.

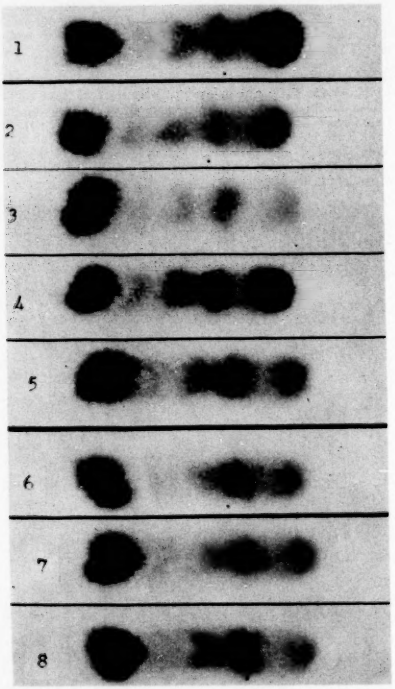

FIGURE 7. *Electrophoretic Patterns of the Serums Tested in Figure 8A and B.*

The serums tested were as follows: 1, C.S.; 2, McK. (a patient with hepatosplenomegaly secondary to chronic hepatitis); 3, P.P. (a patient with eosinophilia, pulmonary infiltrations and ascaris ova in the stools on repeated examinations); 4, N.S.; 5, B.S.; 6, Mr. S. (father); 7, Mrs. S. (mother); and 8, J.S. (sister nine months of age who had no features of the visceral larva-migrans syndrome). Serums 1, 4 and 5 belong to Cases 1, 2 and 3.

CASE 2. C.S., the 2-year-old sister of Case 1, was in excellent health until seven months before admission, when for the 1st time she had wheezing respirations associated with mild rhinitis. There were 4 similar episodes during the last 4 months of 1954. On January 27, 1955, at the time her older sister had her 3d severe episode of pulmonary distress, she had another recurrence of mild wheezing without fever, and both were admitted to a hospital for evaluation. Studies revealed a white-cell count of 32,750, with 65 per cent eosinophils, and hepatosplenomegaly. In view of this and of the previous diagnosis of visceral larva migrans of severe degree made in her sister, she was referred to the Children's Hospital for further study and possible therapy. Her parents reported that, in addition to wheezing, she had had foul-smelling stools, some increased sweating and mild intermittent nausea and vomiting for the preceding 7 months. There had also been considerable dirt eating beginning several months before the onset of the 1st symptoms.

Physical examination revealed a well developed and well nourished girl in no acute distress. The only positive findings were a liver palpable 6 cm. below the right costal margin and a spleen palpable 3 cm. below the left costal margin (Fig. 5). X-ray films of the chest showed a nonspecific increase in perihilar markings and minimal focal inflammatory reaction, chiefly in the right-lung base (Fig. 6).

After preliminary studies (Table 1) the decision was made to try cautiously a therapeutic agent in the hope that if a good response was obtained her sister, N.S., might be similarly treated. She was started on 6 mg. of diethylcarbamazine* by mouth daily and gradually worked up to 30 mg. 3 times daily over a 5-day period, being kept at this level for 10 more days. At no time, however, was there any detectable response to therapy in terms of a change in hepatosplenomegaly or eosinophilia. There were no untoward reactions.

The patient was seen again 2 and 6 months later, when she was entirely asymptomatic but had persistent hepatosplenomegaly, leukocytosis and eosinophilia (counts of over 30 per cent).

CASE 3. B.S., the 4-year-old sister of the 2 previous patients, had been entirely asymptomatic, but had a history of previous pica. Physical examination was considered within normal limits. The liver was palpable 2 cm. below the right costal margin (this was not considered unusual at this age and was the only suggestively positive finding). However, examination of the blood while the family members were being surveyed disclosed a white-cell count of 17,000, with 59 per cent eosinophils (Table 1). Epidemiologic considerations, along with blood smears and laboratory data, including filter-paper electrophoresis of serum proteins (Fig. 7), gamma-globulin determination by immunochemical analysis and a positive precipitin reaction against toxocara antigen (Fig. 8*A* and *B*), provided sufficient data to suggest that this represented a mild case of visceral larva migrans.

DISCUSSION

The literature reveals no previous report of three simultaneous cases in a family. However, it has occurred in siblings, and 3 members of a family in Wisconsin[12] were thought to have had the syndrome; 1 of them had a positive liver biopsy. The 3 cases reported above demonstrate varying degrees of severity of visceral larva migrans, including a nearly fatal case, a mildly ill child with transitory symptoms and an asymptomatic sibling whose diagnosis was made only after a screening blood count.

A biopsy (Fig. 3 and 4) was made of the skin lesions seen in Case 1 during the admission to the Children's Hospital. Microscopical examination of the sections revealed a normal, intact epidermis and appendages. Within the dermis was an inflammatory infiltrate consisting largely of histiocytes and a lesser

*Available as Hetrazan from Lederle Laboratories, New York City.

number of eosinophils. These cells frequently had a perivascular arrangement. There were also occasional areas of fibrinoid degeneration of collagen. No larvae were identified. The sections were seen by several consultants, who commented on certain similarities to Letterer–Siwe disease and dermatomyositis but agreed that no specific diagnosis was possible from microscopical study alone. It was assumed, but not proved, that these changes were due to visceral larva migrans since they paralleled the other clinical manifestations and the rash was similar in appearance to lesions described in visceral larva migrans by others.

bilities. In the first place, the gamma globulin might be elevated because of a specific antibody to toxocara larvae or their products. In such an event one would expect an antigen preparation to make immunologic diagnosis possible since such a large amount of antibody would result in extremely high titers. One would need only to find or devise a suitable test. Secondly, the gamma globulin elevation could be partially or wholly nonspecific, the patients simply being hyper-reactors in this regard—that is, they might show a gamma-globulin increase of similar degree to other antigens or allergens. Finally, the hypergammaglobulinemia might be secondary to al-

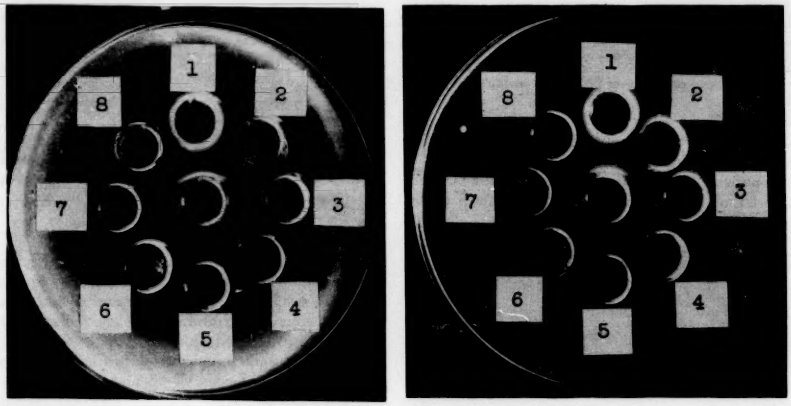

FIGURE 8. *Precipitation Reaction in Gel (Serum Specimens Arranged at Random in "Antibody Reservoirs" Located Concentrically about a Central Reservoir Containing Toxocara Antigen).*

Precipitation has occurred only between the antigen and the serums (1, 4 and 5) belonging to Cases 1, 2 and 3. The precipitate can be recognized by attention to the area near the central reservoir. In A *the reaction is readily seen opposite serum 1 and immediately adjacent to the central reservoir, but is just forming midway between the antigen source and serums 4 and 5.* B *shows the zones of precipitation, which subsequently became clearly evident opposite serums 4 and 5, to have joined to form a single band with a final location near the central reservoir. This is proof of the identical nature of the precipitins present in these serums.*[15] *There is, furthermore, a tendency to coalescence of the bands opposite 1 and 4, suggesting their immunologic identity. Note also the relation between the times of appearance of, as well as the distances of, the precipitate from reservoirs 1, 4 and 5, and the gamma-globulin levels determined electrophoretically (Fig. 7), both of which are related to the precipitin concentration in the separate reservoirs. This technic was repeated with the use of toxocara antigen obtained from ascarids of a different dog with precisely similar results. (Numbering of the serums corresponds to that in Figure 7.)*

Unusual eosinophils (Fig. 9) were found in the peripheral blood in all 3 cases and in the bone marrow of the 2 patients who had this examination. Many of the cells were large, with vacuolated cytoplasm, and had granules that were more sparse than normal and varied remarkably in size and eosinophilic-staining qualities. Unusual eosinophils were also described in Löffler's syndrome in 1939.[13]

Electrophoretic analysis of the serum proteins (Fig. 7) revealed elevated gamma globulins in each case. This finding was confirmed by immunochemical determinations and originally suggested several possi-

tered liver function, or there might be a similarity between this condition and other disorders characterized by hypergammaglobulinemia — for example, the patients described by Janeway et al.[14]

One wonders also about the nature of the stimulus to gamma-globulin production, and the relation, if any, between this stimulus and the marked eosinophilia. Studies are now under way to determine, if possible, the answers to some of these problems. Preliminary work indicates that there is production of specific antibodies, which are detectable in reproducible manner with the use of a saline extract of emulsified adult toxocara worms as the source of

antigen.* Figures 8*A* and *B* show bands of precipitation opposite the serums of the 3 patients described above, whereas there is no visible precipitation opposite the serums of 3 other family members or of 2 other patients tested. Although these studies strongly suggest that the syndrome described in the 3 sisters was in fact caused by *T. canis* infection, it is emphasized that definite immunologic proof awaits exclusion of infection by another parasitic invader having antigens capable of reacting with the patient's serum, to which the toxocara antigen used could be cross-reacting. Methods for further delineating the specificity of the reaction reported are presently under investigation.

TABLE 1. *Pertinent Laboratory Data.**

SUBJECT OF TEST	HEMOGLOBIN	WHITE-CELL COUNT	EOSINOPHILS		BONE-MARROW EXAMINATION	CEPHALIN FLOCCULATION	TOTAL SERUM BILIRUBIN	SERUM ALBUMIN
	gm./100 ml.		%	*per cu. mm.*			*mg./100 ml.*	*gm./100 ml.*
N.S.	11.3	8,350-20,850	18-67	4,418	Excess eosinophils	Positive	0.32	4.52
C.S.	9.8	24,400-38,100	35-61	14,377-24,100	Excess eosinophils	Positive	0.20	3.82
B.S.	12.5	16,000	59	—§	—§	—§	—§	—§
J.S. (sister)	11.5	6,800	2	—§	—§	—§	—§	—§
Father	13.5	8,500	1	—§	—§	—§	—§	—§
Mother	14.0	7,200	1	—§	—§	—§	—§	—§

*Other procedures (urinalysis, tuberculin skin test, skin test for fungi, cultures & various chemical tests) negative; examination of small specimen of backyard soil showed 1 intact toxocara ovum.
†Precipitation reaction in gel.
‡Skin-test antigens obtained from Dr. R. C. Jung, Tulane University, New Orleans.
§Not done.
¶Six specimens.

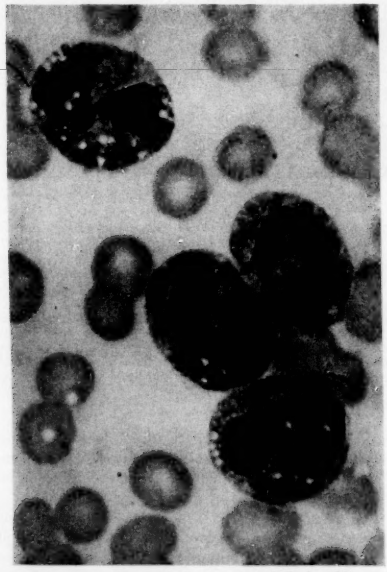

FIGURE 9. *Unusual Appearance of Eosinophils.*

*Modifications of the technics of Ouchterlony and Oudin,[18] utilizing the principles of antigen-antibody precipitation in gel, have been employed.

Differential Diagnosis

In most cases the important differential diagnoses can be made by relatively simple means. Human ascariasis is thought to cause a similar but more transient eosinophilia and pulmonary infiltration.[1,4] It is usually recognized by the presence of ova in the patient's stool (not found in isolated *T. canis* infections) although the exact significance of such a finding is not clear. It is possible, for example, for persons who have human ascariasis to have simultaneous, unrecognized toxocara infection since the conditions necessary for infection are very similar — embryonated ova of *Ascaris lumbricoides* and *T. canis* may coexist as soil contaminants. Eosinophilic leukemia should become apparent on study of the bone marrow, but this may require several examinations and differentiation may be almost impossible in its early stages. There are obvious similarities between visceral larva migrans and so-called "familial eosinophilia." One should consider infection with ascarids or other parasites in all such patients. Likewise, visceral larva migrans is one cause of Löffler's syndrome, which could easily have been the diagnosis made in the first 2 of these patients if toxocara infection had not been considered. Other reported causes of Löffler's syndrome are human ascaris infection, strongyloidiasis, human, dog and cat hookworm infections,[4] pulmonary acariasis due to inhalation of mites,[16-18] atopic allergic phenomena, serum sickness and drug reactions. One could add to this list tuberculosis, brucellosis, trichuriasis, amebiasis and coccidioidomycosis,[4] and probably other disorders, especially those involving hypersensitivity.

The diagnosis of visceral larva migrans should be

considered in patients with persistent or marked eosinophilia, recurrent wheezing associated with pulmonary infiltration, hepatomegaly of undetermined nature, ocular disorders of obscure etiology, unexplained central-nervous-system disturbances, including convulsions, and hypergammaglobulinemia.

TABLE 1 *(Concluded).*

SUBJECT OF TEST	SERUM GLOBULIN	IMMUNOLOGIC TEST FOR TOXOCARA†	SKIN TEST FOR ADULT ASCARIS‡	SKIN TEST FOR ADULT TOXOCARA‡	SKIN TEST FOR LARVAL ASCARIS‡	STOOL EXAMINATION FOR OVA
	gm./100 ml.					
N.S.	3.48	Positive	Positive (+++)	Positive (++)	Negative	Negative¶
C.S.	5.66	Positive	Positive (++++)	Positive (++)	Negative	Negative¶
B.S.	—§	Positive	—§	—§	—§	—§
J.S. (sister)	—§	Negative	—§	—§	—§	—§
Father	—§	Negative	—§	—§	—§	—§
Mother	—§	Negative	—§	—§	—§	—§

*Other procedures (urinalysis, tuberculin skin test, skin test for fungi, cultures & various chemical tests) negative; examination of small specimen of backyard soil showed 1 intact toxocara ovum.

†Precipitation reaction in gel.

‡Skin-test antigens obtained from Dr. R. C. Jung, Tulane University, New Orleans.

§Not done.

¶Six specimens.

Treatment

Current thoughts about prevention and treatment have recently been discussed by Smith and Beaver.[5] There is no therapy of proved value for fulminating respiratory embarrassment found in visceral larva migrans. It seems reasonable, however, to administer oxygen, to provide coverage with broad-spectrum antibiotics, to try epinephrine and possibly to use ACTH or steroids if the condition of the patient is deteriorating, with the thought of ameliorating any hypersensitivity reaction that may be involved. Cautious trials of various tissue anthelmintics seem warranted in patients with chronic disability or recurrent episodes of distress. The possibility of causing an exacerbation in the form of a Herxheimer-like reaction because of rapid killing of many larvae should be borne in mind with any such therapy, however. One should also remember that if repeated exposure to embryonated larvae is prevented, the great majority of patients will recover without treatment.

Measures of probable value in preventing subsequent exposure to ova are: removal of the infected dog or cat from the household or, as a second choice, frequent deworming under the supervision of a veterinary physician; plowing or turning under of soil with which the child might come in contact near the house — this will decrease the number of viable ova available for contact with the hands; provision of a well rounded diet, with judiciously timed offerings of toast, cookies or fruit as desired by the child — this will occasionally provide a satisfactory substitute for dirt eating; attempts to alleviate the stress of emotionally disturbing factors that might condition pica, if such factors are recognized in the child's environment; and recommendation that the child be temporarily transferred, or the family permanently moved, to a new area if this seems to provide an acceptable solution in selected cases.

SUMMARY AND CONCLUSIONS

Three siblings are described who demonstrated varying degrees of severity of the syndrome usually referred to as visceral larva migrans.

Skin manifestations in 1 patient are described and documented with photographs as well as photomicrographs of a biopsy.

Unusual morphology of the eosinophils was demonstrated in each patient.

Marked hyperglobulinemia was found to be largely due to an increase in the gamma-globulin fraction. Preliminary studies suggest that this may be the result — in part, at least — of the formation of specific antibodies.

Visceral larva migrans, a syndrome most often seen in children one to four years of age, is usually manifested by leukocytosis, eosinophilia, hyperglobulinemia, hepatosplenomegaly and pulmonary infiltrations. Occasionally, it causes serious respiratory, central-nervous-system or eye involvement. The diagnosis can be made with considerable certainty on the basis of the clinical picture alone, especially if there is a history of pica in a child who has a dog or cat in the household, and with even more assurance by the finding of fertile toxocara ova in the soil or in the feces of suspected animals. Immunologic tests give promise of enabling specific diagnosis in the near future.

Since this paper was submitted for publication, it has been found that serum from each of the 3 sisters described above possesses "incomplete" (not readily neutralizable by Witebsky substance) anti-A and anti-B activity detectable by the usual tests in serum dilutions of 1:1024 or more. (Anti-A and anti-B titers were kindly determined under the direction of Dr. Fred H. Allen, Jr., by the Blood Grouping Laboratory, Children's Medical Center, Boston.) Such activity was not present to anything like this degree in the control serums shown in Figures 7 and 8. This activity is completely removed by absorption with emulsified adult

toxocara worms (as are anti-A and anti-B from a wide variety of patients and normal subjects). Such absorptions cause no detectable alteration in the electrophoretic patterns of the serums tested, indicating that the proteins removed represent only a small fraction of the total serum proteins. The possibility that encysted toxocara larva or similar parasites act as stimuli to the production of hemagglutinins may be of importance.

We are indebted to the members of the staff of the Children's Hospital, who showed interest in the studies carried out on these patients and encouraged this report, especially indebted to Dr. David Gitlin for his suggestion that Ouchterlony's technic might provide answers to some of our questions, to Dr. Hans Habich, who helped perform the immunologic tests, and to David Coffin, veterinary pathologist, of Angell Memorial Animal Hospital, Boston, who kindly identified and supplied the dog ascarids used in the preparation of the antigen for this study.

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EFFECTS OF PROLONGED CORTISONE THERAPY ON THE STATURAL GROWTH, SKELETAL MATURATION AND METABOLIC STATUS OF CHILDREN*

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BOSTON

OBSERVATIONS on children suffering from Cushing's syndrome have indicated clearly that adrenocortical steroids of the cortisone type may have a marked tendency to suppress growth.[1,2] The present study was undertaken, therefore, when it became apparent that the symptomatic relief afforded patients by cortisone might result in the prolonged administration of this hormone to growing children. The chief purpose of the study has been to determine if possible what effect long-continued cortisone therapy might be expected to have on ultimate stature and metabolic status.

Material and Methods

The patients studied were children receiving cortisone because of adrenocortical virilism, panhypopituitarism, hypoadrenocorticism or severe allergic disorders (Table 1). These children have been observed at intervals of one week to three months in the clinics for children at the Massachusetts General Hospital during the past four years. At each visit, height was determined by one of the authors in a standardized manner[3] with the patient's heels, buttocks, shoulders and occiput touching the measuring stick and with the line formed by the external orifice of the ear and the lower border of the bony orbit perpendicular to the stick. The recumbent position was used to determine body length in patients under three years of age‖; all others were measured in the standing position. Weights were obtained with the child completely undressed or clothed only in light undergarments. X-ray films of the hands and wrists were obtained and compared to the standards of Greulich and Pyle[4] for estimation of bone age. In an effort to be as objective as possible, the films were read by three of us independently without knowledge of the name or status of the patient under consideration. The values set forth here represent the average of

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‖When the initial measurement was obtained with the patient recumbent, all subsequent measurements were carried out similarly.

these readings; in no case were there gross discrepancies between the individual values making up these averages.

The pH and the concentrations of sodium, potassium, chloride, carbon dioxide, nonprotein nitrogen, sugar, calcium, phosphorus, alkaline phosphatase and protein-bound iodine in the serum and the urinary content of 17-ketosteroids were measured periodically

TABLE 1. *Types of Patients Studied and Duration of Treatment.*

DIAGNOSIS	NO. OF PATIENTS	PATIENT MONTHS OF TREATMENT	
		AVERAGE	RANGE
Adrenocortical virilism	11	36.0	12-51
Hypopituitarism	3	8.0	5-14
Addison's disease	2	24.0	17-31
Allergy (endocrine-normal patient)	20	14.5	3-25

with the aid of procedures listed elsewhere.[5] Electrocardiographic tracings were also obtained from time to time for the purpose of observing changes in the T waves.

The children were allowed a normal diet of their own choosing; 3 were given supplements of potassium chloride. Chemotherapy was given only on therapeutic

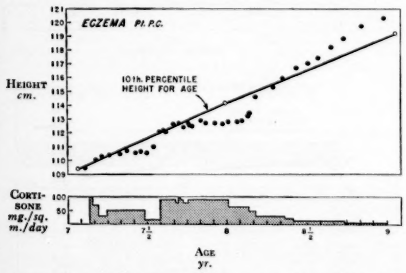

FIGURE 1. *Detailed Observations on the Effects of Administration and Withdrawal of Cortisone Therapy on the Statural Growth of an Eczematous Child.*

indication. Cortisone was administered orally, the total daily dosage being divided into two or three portions. The average and the range of duration of cortisone therapy are indicated in Table 1.

OBSERVATIONS AND COMMENTS ON STATURAL GROWTH AND SKELETAL MATURATION

Figure 1 shows the manner in which an individual patient was followed and the detailed nature of the growth data obtained. Each black circle in the upper section represents a height measurement obtained at approximately two-week intervals according to the chronologic scale covering the two years shown along the abscissa. Though these points have not been connected by lines, they describe changes in height in a smooth and systematic manner. The solid line coursing upwards from left to right indicates the tenth-percentile height values for normal children of the same sex and chronologic age. Cortisone dosages are expressed per square meter of body-surface area per twenty-four hours and are indicated by the height of the shaded zone in the lower section of the chart.

During the first month of therapy, the patient's height rose from a level slightly below to a level slightly above the tenth-percentile line. During the ensuing three and a half months, however, she grew hardly at all and therefore lost position in relation to the tenth-percentile reference line. When, at the age of seven and a half years, the dosage of cortisone was reduced from 50 to 20 mg. per square meter of body-surface area per day, there was a striking growth spurt, during which she regained her initial position on the tenth-percentile line. This sequence of growth suppression with heavy dosages and rebound with reduction in dosage of cortisone is seen again in the twelve-month period shown to the right. These observations thus show that changes in growth rate after institution and withdrawal of cortisone may be detected within a few weeks by means of meticulously performed, frequently repeated measurements.

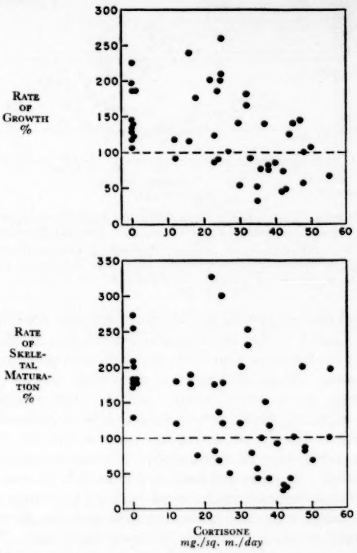

FIGURE 2. *Effects of Cortisone at Various Dosage Levels on the Rate of Growth (per Cent of Normal for Bone Age) and Rate of Skeletal Maturation (per Cent of Normal) of Children with Congenital Adrenocortical Virilism.*

Figure 2 is concerned with relations between corti-

sone dosage, rate of statural growth and rate of skeletal maturation in a group of patients with congenital adrenocortical virilism. Here, cortisone doses are shown along the abscissal scale. In the upper section, the ordinate scale along the left-hand border gives rate of growth expressed as percentage of average

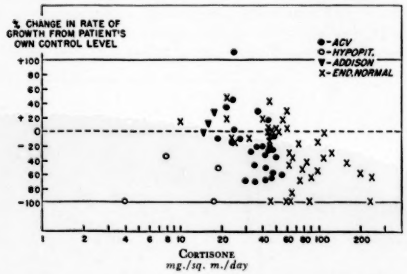

FIGURE 3. *Difference in Responsiveness to Growth-Suppressing Effects of Cortisone in Patients with Various Conditions. ACV = adrenocortical virilism; hypopit. = hypopituitarism; Addison = hypoadrenocorticism; and end. normal = endocrine-normal patients.*

expected for persons of the same sex and bone age. The points in the upper section located directly above zero dosage show that these children were growing at between 100 and 225 per cent of average normal rate during pretreatment, control periods. The points to the right of these control values show a downward trend indicative of decreasing rates of growth with increasing doses of cortisone for the majority of these patients. In these children, approximately 35 mg. of cortisone per square meter of body-surface area per day was required to reduce growth rates to average normal levels for persons of equal bone age. The lower section of the figure shows that cortisone had a similar tendency to reduce rate of skeletal maturation.

Figure 3 is concerned with differences in the responsiveness of patients with various conditions to the statural-growth-suppressing effects of cortisone. The types of patient presented here are revealed by the symbols with explanatory notations at the top right of the chart. Changes in rate of growth, expressed as a plus or minus per cent deviation from the patient's own control level per the ordinate scale, are plotted against cortisone dosage as shown along the logarithmic abscissal scale. It can be seen that doses of cortisone ranging between 4 and 20 mg. per square meter of body-surface area per day had a marked growth-suppressing effect only in the hypopituitary subjects; they may have prompted a slight increase in the growth rate of certain patients with Addison's disease and adrenocortical virilism and those who were endocrine normal but allergic. Doses of 30 to 50 mg. caused a 20 to 70 per cent reduction in the rate of growth of the majority of the patients with adrenocortical virilism. Finally, doses in excess of 60 mg. caused a 20 to 100 per cent reduction in the growth rate of the endocrine-normal subjects.

It may be seen from the growth chart of Figure 1 that the eczematous patient represented there underwent a marked growth spurt after cortisone dosage had been reduced. Figure 4 considers this phenomenon in 2 other patients. In the uppermost section the rate of growth of a girl with nutritional dwarfism is plotted in terms of centimeters per year per the ordinate scale against actual age in years per the abscissal scale. When cortisone was given in heavy doses, growth slowed to a standstill. Reduction of dosage to approximately 30 mg. per square meter of body-surface area per day was followed by a major upswing in growth rate. The same phenomenon is illustrated in the lower section of the figure by data obtained on a boy with severe asthma. These findings indicate that it is not necessary to eliminate cortisone therapy altogether to make it possible for patients to undergo a compensatory growth spurt. Rather, it appears that such a spurt may take place when cortisone dosage simply is reduced appreciably below growth-suppressing levels.

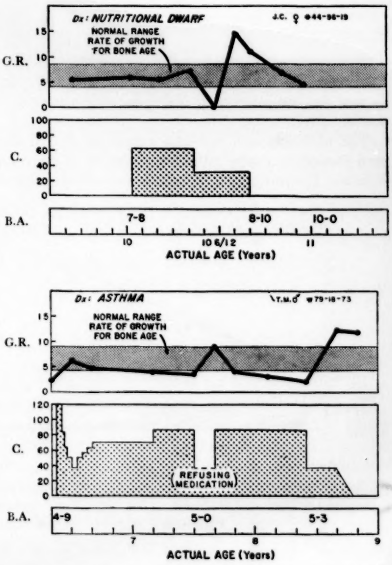

FIGURE 4. *Suppression of Growth Rate with High Dosages of Cortisone; Recovery with Growth Spurt on Reduction of Dosage.*

G.R. = growth rate (cm. per year); C = cortisone (mg. per square meter per day); and B.A. = bone age (in years).

Figure 5, which is of the same design as Figure 4, shows that the compensatory or rebound phenomenon observed in most patients on reduction of cortisone dosage below growth-suppressing levels is absent in hypopituitary patients. This, coupled with previous observations, makes one wonder whether pituitary-growth factors may be stored in potentially active form during periods when growth is being suppressed by cortisone.

Figure 6 gives information concerning changes in the ratio of height age to bone age during prolonged intervals of cortisone therapy. It may be assumed that a gain in height age in relation to bone age should be followed if anything by a gain in ultimate stature. Contrariwise, it is to be expected that a loss in the ratio of height age to bone age signifies a tendency to decreased ultimate stature.

Along the left-hand ordinate of each of the three main sections is a scale giving values for the ratio of

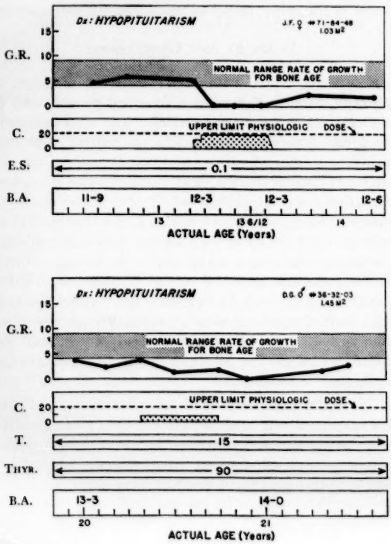

FIGURE 5. *Absence of Growth Spurt after Cessation of Cortisone Therapy in the Hypopituitary Patient.*
G.R.=growth rate (cm. per year); C.=cortisone (mg. per square meter per day); E.S.=estrone sulfate (mg. per square meter per day); B.A.=bone age (in years); T.=testosterone (mg. per square meter per day); Thyr.=thyroid (mg. per square meter per day).

height age to bone age whereas the chronologic ages of patients is given by the abscissal scales. The left hand of each pair of points connected by a solid black line indicates the position of an individual patient at the onset of cortisone therapy, and the right hand point represents his or her position after a period of continuous or semicontinuous cortisone treatment. The light, interrupted horizontal lines originating at the ratio 1.0 of the ordinate scale indicate the positions where one would expect points to fall if a person at all chronologic ages was of exactly average height for bone age.

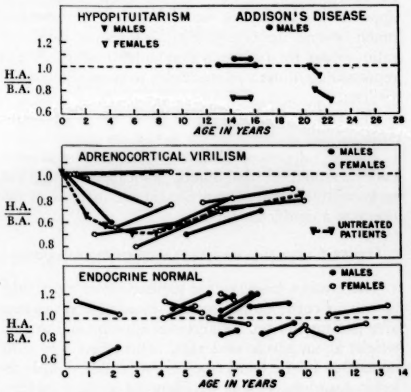

FIGURE 6. *Over-All Changes in the Ratio of Height Age (H.A.) to Bone Age (B.A.) during Prolonged Cortisone Therapy.*

In the top section of the figure, it should be noted that the lines for the patients with Addison's disease are horizontal, indicating maintenance of *status quo* during the period of cortisone treatment. By contrast, although the younger of the hypopituitary patients similarly maintained *status quo*, the 2 older patients lost height in relation to skeletal maturation as evidenced by the downward slope of the lines representing them. It should be recalled, as shown in Figure 5, that the younger female pituitary patient also was receiving small doses of estrogen and thyroid and that the older male patients were being given small doses of testosterone and thyroid.

In the patients with adrenocortical virilism, plotted in the middle section of Figure 6, it is necessary to view the changes in ratios of height age to bone age that took place during cortisone therapy in relation not only to the lighter, horizontal, interrupted reference line representative of average normal progress but also to the heavier, interrupted reference line indicating in approximate terms the average ratios of height age to bone age found in a control group of children with adrenocortical virilism who had not been treated with cortisone. This heavier line shows that the ratio values of untreated patients with adrenocortical virilism tend to fall sharply during the first four years of life and subsequently to rise toward normal levels. In 3 of the 4 cases in which cortisone

therapy was started before six months of age, the ratio values lie appreciably above the curve representing untreated patients. This suggests that it may be possible to prevent the dip in values for ratios of height age to bone age observed in the first four years by institution of therapy during early infancy. It appears that delay in administration of cortisone much beyond the first year or so does not cause the ratio values to deviate appreciably from the curve representing untreated children with adrenocortical virilism.

The ratios of height age to bone age of the endocrine-normal patients shown in the lowermost section of Figure 6 decreased in about a third of the patients and increased in the others. On the average the ratios of this group of patients did not increase or decrease to a significant extent.

Other Clinical and Laboratory Observations

There was a tendency for patients given more than 50 mg. of cortisone per square meter of body-surface area per day to have an increased appetite and to gain weight at an accelerated rate. This effect was most noticeable in the endocrine-normal children with allergic disorders. It also was observed in the panhypopituitary patients at times when they were taking as little as 10 to 20 mg. of cortisone per square meter per day. Those whose weight increased 30 to 60 per cent above pretreatment levels tended to show the ruddy complexion and full facies characteristic of Cushing's syndrome. With the exception of 1 of the hypopituitary patients whose blood pressure rose to 140 systolic, 100 diastolic, while he was receiving 18 mg. of cortisone per square meter per day, none of the present series of patients became hypertensive.

Breast development took place in 4 girls of the endocrine-normal group. The breast development of the oldest 2, whose actual ages were twelve and eleven years and whose bone ages were eleven and ten and a quarter years, respectively, persisted after cortisone treatment was discontinued. In the 2 younger girls of this group, with chronologic ages of seven and one years and with bone ages of five and a half and one years, respectively, the breast tissue that had developed while the patients were taken cortisone disappeared completely after cessation of therapy. Breast development also was noted in 6 girls with congenital adrenocortical virilism. Five of these children were between five and nine years of age chronologically; the other was fourteen. The bone ages of these patients ranged between eight years in the youngest and seventeen years in the oldest girl. Only the oldest girl has had menstrual periods, which had started when she was fourteen and a half years old.

A total of more than 300 determinations of serum sodium, potassium, calcium, chloride, carbon dioxide, phosphorus, phosphatase, sugar and protein-bound iodine were performed. With the exceptions noted below, all these determinations yielded normal results. Two children of the endocrine-normal group manifested hyponatremia (sodium levels of 126 and 129 milliequiv. per liter), and 1 patient with adrenocortical virilism had hypernatremia (level of 172 milliequiv. per liter) when seen with an acute febrile illness two or three days after abrupt discontinuation of cortisone therapy by their parents. One of the hyponatremic patients was also mildly hypokalemic (serum potassium of 3.8 milliequiv. per liter) and had depressed electrocardiographic T waves and a blood sugar of 33 mg. per 100 ml. Two of the children whose growth rate was strikingly suppressed showed low values for serum alkaline phosphatase — namely, 3.4 and 2.8 Bodansky units.

A total of 65 electrocardiograms were obtained on 22 of the patients. With the exception mentioned above, none showed significant abnormalities of the sort seen in patients with potassium deficiency or potassium intoxication. Roentgenograms, including those of the spine, failed to reveal definite osteoporosis.

Summary and Conclusions

Cortisone tends, within a few weeks of onset of therapy, to slow the rates of statural growth and of skeletal maturation of children. The dose required to produce these effects differs in children with certain conditions. As little as 4 to 20 mg. per square meter of body-surface area per day has had a marked growth-suppressing effect on hypopituitary patients. About 35 mg. per square meter a day was needed to reduce the rate of growth of patients with adrenocortical virilism from supranormal to average normal levels; administration of 35 to 50 mg. per square meter per day tended to reduce their rates of growth and skeletal maturation to subnormal levels. A minimum of 45 mg. per square meter per day was required to reduce the growth rate of endocrine-normal children.

With the exception of the hypopituitary patients, there was a strong tendency for children given growth-suppressing doses of cortisone to undergo a compensatory growth spurt when dosages were reduced below growth-suppressing levels or were eliminated altogether. When given in dosages sufficient to cause a reduction in growth rate to subnormal levels, cortisone also was apt to produce facial changes and obesity of the type seen in patients with Cushing's syndrome.

Though numerous chemical measurements and electrocardiographic tracings were obtained, only a few abnormalities were found. These occurred in 3 patients whose cortisone therapy had been discontinued abruptly by their parents when acute febrile illnesses developed. No osteoporosis was evident in roentgenograms of the long bones or spine.

It is tentatively concluded that cortisone can be administered over considerable periods to growing

children without necessarily altering the child's potential ultimate stature. For hypopituitary patients, the dosage used must be kept very low lest growth be inhibited altogether. In the child with Addison's disease physiologic substitution dosages appear to be without appreciable effects on either growth or maturation. For children with congenital adrenocortical virilism, it appears desirable to start the hormone early and to administer it continuously in doses sufficient to reduce rates of skeletal growth and maturation to average normal levels. Finally, for endocrine-normal children who have not attained sexual maturity, it seems essential to reduce dosages below growth-suppressing levels from time to time to permit them to regain ground lost during intervals of relatively heavy dosage before the age when recovery of statural position is precluded by closure of skeletal epiphyses.

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CORRELATION OF GROSS GASTROSCOPIC FINDINGS WITH GASTROSCOPIC BIOPSY IN GASTRITIS*

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BOSTON

THE development of the Wolf–Schindler flexible gastroscope in 1932[1] followed by the Benedict flexible operating gastroscope in 1948[2] and the flexible gastric-biopsy tube invented in 1949 by Wood et al.[3] has stimulated a great deal of interest in gastritis. Although a previous attempt at correlation of gastroscopic and pathological findings in gastritis was made by Benedict and Mallory[4] in 1943, the study was based not on biopsy but on surgical specimens resected for ulcer or carcinoma. As soon as gastroscopic biopsy became available it was evident that the concept of gastritis had to be revised. In 1949 Benedict[5-7] stated that "reddening, edema, and adherent secretion may be present in a gastric mucosa that shows no significant histologic change" but that "there may be pathological evidence of gastritis in a stomach that looks normal to the endoscopist." Again, in 1951, Benedict[8] made the following comment:

> . . . it is already apparent that the clinical appearance of severe gastritis is not always substantiated by histologic evidence. In some cases, on the other hand, a relatively normal appearing stomach may show pathologically a considerable degree of gastritis.

Subsequently, the same author[9] expressed the opinion "that no gastroscopic examination is complete unless biopsy under direct vision is available." The necessity for revising the present concept of gastritis has recently been emphasized by Benedict and Atkins.[10]

This study is an attempt to correlate the gastroscopic appearance of so-called hypertrophic, superficial and atrophic gastritis, as well as that of the normal mucosa, with the microscopical findings in each case. Gastroscopically hypertrophic or chronic gastritis was thought to be characterized by a verrucous appearance of the gastric mucosa, which Benedict and Mallory[4] considered to be represented microscopically by an exaggeration of the chronic inflammatory infiltrate normally found in nearly every stomach. An inflammatory band occupying a third or more of the width of the gastric mucosa was considered pathologic except in the antrum, where such a band was regarded as evidence of disease only if it involved at least half the width of the mucosa (Fig. 1 and 2).

Superficial gastritis has been diagnosed gastroscopically by the presence of increased reddening, edema and adherent secretion. Microscopically, an infiltrate of polymorphonuclear neutrophils is seen in the interstitial tissue of the upper portion of the gastric mucosa. This is the acute gastritis as observed by the pathologist (Fig. 3 and 4).

Atrophic gastritis, or gastric atrophy, is seen gastroscopically as a pale, thin mucosa with visible blood vessels. Histologically, there is intestinal metaplasia and a variable degree of chronic inflammatory infiltrate and loss of the glandular portion of the mucosa (Fig. 5).

Material and Methods

During the period from March, 1948, to June, 1954, a total of 401 gastroscopic examinations were performed on 370 patients at the Massachusetts Gen-

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eral Hospital; 391 biopsies were done, 258 of which concern the present study of gastritis. Most of the remainder were obtained from neoplasms or from what were thought to be neoplasms by the gastroscopist and from the edges of peptic ulcers. Stomachs considered normal by the gastroscopist, as well as

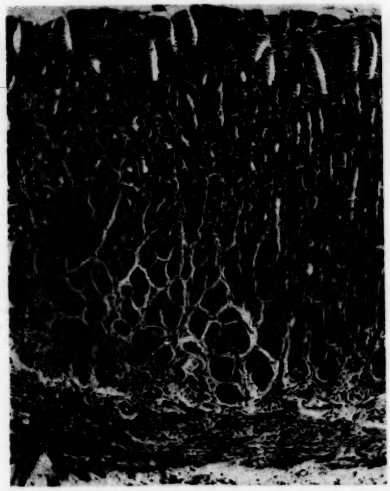

FIGURE 1. *Typical Normal Gastric Mucosa (X85). Note the adequacy of the biopsy specimen, which includes the muscularis mucosae.*

those in which a gastroscopic diagnosis of gastritis was made, are included. No distinction is made among postoperative stomachs, cases associated with gastric or duodenal ulcer, polyps or cancer. Only biopsied areas are considered, although other lesions may have been found in the same stomach by means of the gastroscope.

In all cases the Benedict operating gastroscope was used, and the great majority of these procedures were carried out by one of us (E.B.B.). One complication, a perforation on the lesser curvature, occurred in a seventy-seven-year-old woman. This was sutured at laparotomy, and the patient was discharged well thirteen days later.

The biopsy specimen obtained in each case usually ranged from 3 to 5 mm. in diameter and provided a full thickness of mucosa, including the muscularis mucosae in many cases. For the most part the specimens were quite adequate for pathological interpretation. Among the 258 biopsies considered for the gastroscopic-histologic correlation of gastritis, 19 were discarded. Most of these discarded specimens contained inadequate tissue. Some specimens showed only esophageal mucosa in cases biopsied in the region of the gastric cardia. The gastroscopist realized in several cases that he might have taken esophageal tissue rather than gastric mucosa.

RESULTS

The results are summarized in Table 1, which shows that 62 out of 71, or 87.3 per cent, of specimens considered normal by the gastroscopist showed histologic agreement.

Of 30 cases considered chronic gastritis at gastroscopy only 2 showed a pathologic increase of the chronic inflammatory band. Twenty-three, or 76.7 per cent, were normal microscopically.

Seventy-eight specimens were taken from areas thought to show acute gastritis; microscopically, 48, or 61.5 per cent, of these were normal, and 13, or 16.7 per cent, showed acute gastritis. In addition to

FIGURE 2. *Microscopical Appearance of Chronic Gastritis (X 85). Note the numerous chronic inflammatory cells throughout the entire thickness of the mucosa.*

acute gastritis, 6 specimens demonstrated atrophy, and 3 chronic gastritis.

Nineteen cases of atrophy were seen gastroscopically. Eight, or 42.1 per cent, showed atrophy microscopically. Nine, or 47.4 per cent, were normal.

In 41 specimens the gastroscopic impression was both acute and chronic gastritis. Four showed complete histologic agreement, and 10 either acute or

chronic gastritis, and 22, or 53.7 per cent, were normal.

Discussion

The strikingly poor correlation between the gastroscopic diagnosis of chronic gastritis and its microscopical counterpart corroborates the findings of others. Of the 27 out of 30 biopsies giving no correlation in our series, 23 showed a normal microscopical picture. Palmer[11] obtained 42 normal biopsies out of 53 specimens thought to be hypertrophic gastritis. Ylvisaker et al.[12] reported microscopically normal mucosa in 11 of 12 cases diagnosed as hypertrophic gastritis at gastroscopy. Normal mucosa was found in 3 out of 9 cases thought to be hypertrophic gastritis at gastroscopy by Selesnick

Figure 3. *Microscopical Appearance of Acute Gastritis (X 85).*

and Kinsella.[13] It thus appears evident that the previous concept of hypertrophic gastritis must be revised. Palmer[11] and Ylvisaker et al.[12] conclude that the verrucous appearance of the gastric mucosa represents some unusual physiologic state. It seems that one must probably consider the verrucous nature of the mucosa to be within normal limits. Joske, Finckh and Wood,[14] in an excellent study of 1000 consecutive gastric biopsies obtained by the flexible gastric-biopsy tube, found, in 258 cases in which gastroscopy was also performed, "little correlation between gastroscopic appearances and histologic findings."

The gastroscopic-histologic correlation in acute gastritis was likewise disappointing. Forty-eight out of 78 cases (61.5 per cent) with no correlation

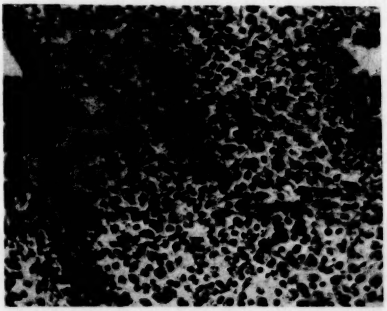

Figure 4. *Enlargement of Figure 2, Showing Acute Gastritis with Numerous Polymorphonuclear Neutrophils (X 270).*

showed a normal mucosa microscopically. Ylvisaker et al.[12] found no cases that they could identify as

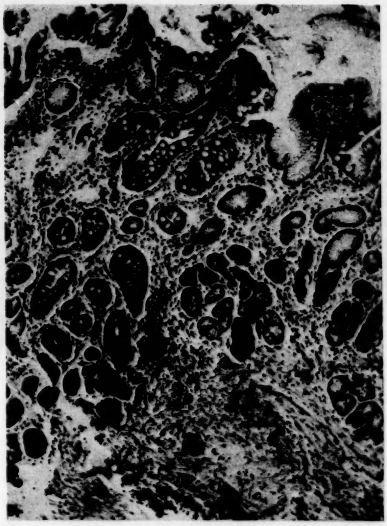

Figure 5. *Microscopical Appearance of Gastric Atrophy (X 85).*

Note the thinning of the mucosa, with intestinal metaplasia and marked diminution in the number of gastric glands.

superficial gastritis at gastroscopy, and yet 8 of 77 biopsy specimens proved to be acute gastritis. Selesnick and Kinsella[13] diagnosed 8 cases as superficial

gastritis at gastroscopy. Microscopically, 2 of these showed chronic gastritis, and 6 acute and chronic gastritis. Some of the normal biopsy specimens in our series may be accounted for by the patchy nature of the changes described in many cases, but this alone could hardly explain the wide discrepancy. The concept of superficial gastritis thus does not appear to be that of a clear-cut entity. Our results suggest that the presence of increased mucosal reddening, presumably caused by vascular congestion, which

TABLE 1. *Comparison of Gastroscopic and Microscopical Diagnoses in 239 Cases.*

Gastroscopic Impression	Total Biopsies	Microscopical Impression				
		Normal specimens	Cases of chronic gastritis	Cases of acute gastritis	Cases of atrophy	Cases of acute & chronic gastritis
Normal specimen	71	62	4	0	4	1
Chronic gastritis	30	23	2	4	1	0
Acute gastritis	78	48	8	13	6	3
Atrophy	19	9	2	0	8	0
Acute & chronic gastritis	41	22	7	3	5	4
Total	239					

cannot be evaluated accurately in small biopsy specimens, may not necessarily be accompanied by a polymorphonuclear infiltrate.

Eight biopsy specimens out of 19 diagnosed as gastric atrophy on gross examination disclosed corresponding histologic changes. Two of those not showing atrophy were taken from areas where there were some visible rugae in addition to the pale, smooth mucosa; conceivably, biopsy material taken in the smooth areas would have shown typical gastric atrophy. Two of the 8 cases with good correlation were in patients with pernicious anemia. One patient had had the disease for thirteen years. In the other the diagnosis of pernicious anemia was made during the same hospital admission in which the biopsy specimen was taken. A gastric cancer was diagnosed by x-ray study in this case, and a total gastrectomy for carcinoma was performed four months later. In the series of Ylvisaker et al.[12] a gastroscopic-histologic correlation in gastric atrophy was found in 14 out of 22 cases.

In stomachs showing a combination of acute and chronic gastritis at gastroscopy, histologic correlation was also poor.

Although it is recognized that the stomach is a large organ, and it is realized that a single biopsy may not always be a fair sample, we believe that gastroenterologists must revise their concept of the significance of gross gastroscopic appearances.

Further studies are in progress to correlate if possible the symptomatology of gastritis with x-ray findings, gastroscopic appearances and pathological findings as determined by biopsy.

Summary and Conclusions

Two hundred and thirty-nine gastroscopic biopsy specimens were studied in an attempt to correlate the gastroscopic appearance of gastritis with the microscopical lesion.

In stomachs that appear normal to the gastroscopist, there is a 13 per cent chance that the pathologist will find a significant degree of some type of gastritis. The verrucous appearance of the gastric mucosa thought gastroscopically to be chronic (hypertrophic) gastritis is associated with a normal histologic picture in most cases. This finding indicates that the verrucous nature of the mucosa is probably a normal variant. The term hypertrophic gastritis should therefore be abandoned.

The areas of increased mucosal reddening, with edema and adherent secretion, — recognized by the gastroscopist as superficial gastritis, — usually showed either a normal histologic picture or an acute inflammatory infiltrate, in most cases being normal.

The gastroscopic picture of a mixed acute and chronic gastritis was found to show complete or partial microscopical correlation in about a third of the cases. About half the specimens had a normal microscopical appearance.

It is evident, therefore, that gross gastroscopic appearances are not reliable in the diagnosis of gastritis. For diagnostic accuracy gastroscopic biopsy under direct vision must be done, or tissue must be obtained by the flexible gastric-biopsy tube.

We are indebted to Dr. Benjamin Castleman for his helpful criticism.

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LATE-PREGNANCY BLEEDING AND RUPTURE OF THE MARGINAL SINUS*

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THE primary purpose of this presentation is to describe further the clinical picture of rupture of the marginal sinus of the normally implanted placenta. A general plan for the management of this complication is described.

It is recognized that many physicians and medical communities have been reluctant to accept this really old diagnosis; however, for lack of time, its distinctness is not defended here except for one particular. An explanation is necessary because many have raised the question whether cases of rupture of the marginal sinus are not actually abruptions of the marginal portion of the placenta. They are not, because careful examination of the placenta, the membranes and the clot does not give the impression that the clot has ever been between the uterus and the functioning maternal surface of the placenta. The maternal surface that is adjacent to the clot is not indented. It is not discolored; its surface texture is not altered, and the clot is not adherent to it. The studies of Fish and his associates[1,2] have shown that the formalin-fixed placentas of rupture of the marginal sinus do not have the infarctions typical of abruption. The patients with the diagnosis of rupture of the marginal sinus had none of the pain, tenderness and hypertonicity of the uterus or shock that one associates with abruption.

The diagnosis of rupture of the marginal sinus of the normally implanted placenta was made in the present report only under the following circumstances: the exhibition of a clot at the placental margin that was continuous with clotted blood in the marginal sinus; exclusion of placenta praevia by vaginal examination; and elimination of abruption by the clinical picture and examination of the placenta.

Many cases that actually were rupture of the marginal sinus have in the past been considered marginal abruption or given the confusing title of "mild abruption." For some reason placental abruption at the Charity Hospital hardly ever appears now to have a mild variety, possibly because the diagnosis is made only in cases of bona fide abruption, thus excluding women who bleed from unknown causes or from a rupture of the marginal sinus of the normally located placenta. It is not denied that there is such a condition as an abruption in which only a minor segment of the placental circle has separated; it is also probable that some marginal, and greater, separations follow a rupture of the marginal sinus, especially when the placenta itself is abnormal.

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FREQUENCY OF RUPTURE OF THE MARGINAL SINUS

The basis for my description of rupture of the marginal sinus is 51 cases collected in three and a half years. These cases are not consecutive and are by no means a total sample of the Tulane Service at the Charity Hospital. During this period I first became acquainted with the diagnosis of rupture of the marginal sinus. These are all the proved cases that can be found at present.

I do have a complete and accurate six-month compilation of the women with external bleeding in the latter half of pregnancy, from which one can learn something of the frequency of rupture of the marginal sinus. In the period under discussion there were 2251 deliveries, and all members of the active staff engaged in a daily conscientious collection and description of placentas, discussion of the diagnosis and recording of the cases. Without this approach any analysis of the frequency of various types of bleeding in an obstetric unit is likely to be inaccurate. Dependence on the collection at a later date of diagnoses that eventually appear on the face sheets of the patients' charts will yield deceptive figures. One reason is that the less perilous cases of hemorrhage are lost sight of; rupture of the marginal sinus is usually not a great hazard to mother or baby. All the hemorrhages that occurred in this six-month series were of sufficient degree to justify concern and recording as cases of hemorrhage because in each the patient was examined vaginally, with facilities for blood replacement and cesarean section in readiness.

Estimations in the literature of the frequency of rupture of the marginal sinus range all the way from "an infrequent finding" to "the most common cause" and 39 per cent[2] of the external hemorrhages in the third trimester. The literature and informal discussion lead one to the conclusion that in each year of this decade more cases are being found. The frequencies of the different causes of external hemorrhage that occurred in the six-month period under discussion are given in Table 1. They were collected in the first and third quarters of 1954. The periods selected for these observations were determined by my assignments in the department. There were 97 cases of hemorrhage in late pregnancy in the six-month period, and the most frequent cause was rupture of the marginal sinus of the normally implanted placenta — 33 cases, or 34 per cent of all the cases.

The second most frequent class of hemorrhage was the group, often overlooked and forgotten, of undetermined etiology, which contained 30 cases, or 31 per cent of the total number of cases. Undoubtedly, some of these puzzling cases represented bleeding from ruptures of the marginal sinus, but they did not meet the strict criterion of the exhibition of a clot at the placental margin that was continuous with clotted blood in a sinus. Abruption, cervicitis and placenta praevia were the next most common diagnoses, in that order, and were considerably less common than the first two causes of hemorrhage. Low-lying placenta accounted for 4 cases. In 1 case a circumvallate placenta seemed the only explanation for the bleeding.

Syndrome of Rupture of the Marginal Sinus

Admittedly, an attempt to describe the syndrome of rupture of the marginal sinus with the 51 cases collected is exploratory. Nevertheless, some distinct trends in the make-up of this obstetric accident can be seen. The characteristics of these cases were similar to those noted by Fish and associates[2] and Gainey and Nicolay[3] — a point that seems to solidify the concept of this entity.

Table 1. *Causes of Hemorrhage in 2251 Deliveries (First and Third Quarters of 1954).*

Diagnosis	No. of Cases
Rupture of marginal sinus	33
Cause undetermined	30
Abruption	13
Cervicitis	10
Placenta praevia	6
Low-lying placenta	4
Circumvallate placenta	1
Total	97

First, what sort of woman is likely to have a rupture of the marginal sinus? Race and age apparently have nothing to do with it: 14 per cent of patients were white, and this is the usual figure for the Service; and the average age was twenty-six years. A control group of 200 women picked at random from the years covered by this study also had an average age of twenty-six. Toxemia does not predispose the patient to rupture of the marginal sinus. Ferguson and Miller[4] report toxemia in 19 per cent of cases on the Service. With the use of the same diagnostic criteria 14 per cent of these women who bled from the marginal sinus could be classified as toxemic. After an accumulation of additional cases it may be learned that rupture of the marginal sinus is more likely to occur in a woman who has had an increasing number of pregnancies. Only 7 per cent of the control cases referred to above were in patients in the sixth or later pregnancy, compared with 22 per cent of those with rupture of the marginal sinus.

In this study recurrent bleeding did not seem to be an important feature of rupture. Only 3 women had an appreciable interval between the onset of bleeding and the onset of labor; 1 was a one-day interval, and the other 2 were two-day and four-day intervals, respectively. In private practice, where there is a better continuity in the observation of the individual patient, recurrent bleeding may be more obvious.

The time relation of the first external bleeding to labor takes a certain trend. The bleeding initially appeared in the second stage of labor in only 6 cases. In 19 it began before labor, and in 26 it began during the first stage of labor. In 28 of the 51 cases there was an intimate relation between the onset of labor and the onset of bleeding. Ten women thought the bleeding had begun immediately before labor, and 10 women placed the first bleeding as occurring immediately after the onset of labor. Eight believed that labor and bleeding had begun simultaneously.

In symptoms, as well as in the appearance of the placenta, rupture of the marginal sinus resembled placenta praevia more than abruption. This is not surprising, for the bleeding mechanism in marginal-sinus bleeding is similar to that of marginal placenta praevia and of low-lying placenta; there is not the tissue destruction at the placental site that is generally assumed to be the origin of some of the signs after abruption. None of the patients under discussion had pain, uterine tenderness, hypertonic uterus or shock; nonetheless, it seems inevitable that these signs will appear at some time in some cases.

Table 2. *Appearance of the Blood in 51 Cases of Rupture of the Marginal Sinus of the Placenta.*

Appearance of Blood	No. of Times Observed
Bright red	31
Clots	17
Dark red	11
Not described	10
Total	69

The appearance of the blood lost as described by the different observers is presented in Table 2. More than one of the physical characteristics of blood were noted in some cases, but bright-red blood was the type most frequently seen. The amount of estimated blood loss was over 500 ml. in only 5 of the 51 cases. The blood loss in all the cases is shown in Table 3. Rupture of the marginal sinus with concealed hemorrhage has been found at the Charity Hospital, but a careful, sustained search for this has not been made.

With the loss of a small amount of blood, — and that from the mother, — lack of shock and no interference with the placental-uterine union, one should expect a good fetal-survival record. There was 1 stillborn baby (at twenty-six weeks' gestation). The

3 neonatal deaths were all in premature infants, 1 of them weighing 600 gm.

The tendency for rupture of the marginal sinus to be associated with premature labor is an important observation. The average week of gestation in which these patients were delivered was the thirty-fifth (median, thirty-sixth). Since recurrent bleeding is not a prominent feature the week of delivery and the week in which bleeding began are the same. As might have been expected, 45 per cent of these babies were premature (weights of 2500 gm. or less) — considerably more than the hospital rate of 14 per cent. If this high frequency of prematurity with rupture of the marginal sinus should be evident as larger numbers of cases are studied, this type of bleeding will have to be included as a cause, or consequence, of premature labor. Was the sinus ruptured by preternatural uterine changes and activity, or was the rupture and escape of blood responsible for labor? The placing of the time of the first external bleeding close to the supposed onset of labor in more than half the cases strengthens the suspicion that there is a causal relation.

Other Observations

Some preliminary data that I have collected suggest that the placentas with rupture of the marginal sinus tend to be of larger diameters. Placentas with greater surface areas conceivably have an increased chance of having a margin relatively low in the uterine cavity, without qualifying as low-lying placentas. This inferior margin is exposed to greater stress from the changes in the underlying myometrium than other parts of the placental margin. An earlier observation[5] that the rupture site is located on the same side as the opening in the membranes continues to be made. Related to the large size of the placentas is the fact that 2 of the 51 placentas had well defined accessory lobes, and 2 had unusual conformations that almost formed accessory lobes. It is interesting that there were 2 examples of accessory lobes in the 30 cases of bleeding of undetermined origin that appeared in the six-month study period.

Diagnosis

As yet the diagnosis is positively made only after delivery and examination of the placenta. The likelihood of bleeding from the normally located marginal sinus for a long time before labor is small so that protracted periods in which one can ponder the diagnosis are unusual. During labor the possibility of placenta praevia is ruled out by vaginal examination: by the time vaginal examination is arranged there is usually enough cervical dilatation for that diagnosis or an abnormally low implanted placenta to be ruled out with confidence. Radiologic localization of the placenta might help, but usually the urgency of progress in labor and continued bleeding make this less feasible than vaginal examination. Lack of either faulty presentation or high station of the presenting part may be aids in the presumptive diagnosis of rupture of the marginal sinus. In the cases in this series, abruption was not often seriously considered because of the lack of local and general signs of distress. The concurrence of toxemia and bleeding should certainly cause one to consider abruption carefully.

Management

All the women described in this paper were delivered vaginally. The rarity of recurrent hemorrhage reduced the opportunity to practice expectancy for any great time. Once placenta praevia had been excluded and the lack of signs of abruption confirmed, the patient was allowed to proceed in labor. The management seems to resemble that employed with low implantation more than anything else. Artificial rupture of the membranes has not been tried often enough for one to evaluate its effect; the possibility of tamponade seems less likely than in marginal placenta praevia. In the few cases in which the blood loss was alarming, delivery was so imminent that nothing but vaginal delivery could be considered. If the blood loss had been great enough and the cervical dilatation slight, a cesarean section would have been carried out regardless of the diagnosis, or the uncertainty of the diagnosis: this is blood that the mother can ill afford to lose no matter where it is coming from. If substantial, blood loss should be replaced. If there is considerable doubt whether the diagnosis is rupture of the marginal sinus or abruption it seems safer to treat it as if it is the more treacherous of the two.

TABLE 3. *Estimated Blood Loss in 51 Cases of Rupture of the Marginal Sinus of the Placenta.*

Amount of Blood Lost	No. of Cases
ml.	
<100	12
100 to 500	26
>500	5
—*	8
Total	51

*Not estimated (small amount).

Summary and Conclusions

Some comparisons between rupture of the marginal sinus of the normally implanted placenta and abruption are made. Many cases of rupture of the marginal sinus are being called abruption. Rupture of the marginal sinus may be the most frequent cause of bleeding in late pregnancy.

On the basis of a study of 51 cases the clinical

picture of rupture of the marginal sinus is described. It is not caused by toxemia, and repeated bleeding is uncommon. The bleeding has a tendency to appear first near the onset of labor. Rupture of the marginal sinus is painless, and the amount of blood lost usually does not threaten life. This syndrome is less lethal for the fetus than abruption or placenta praevia but is frequently associated with prematurity. The diagnosis can be made with certainty only by examination of the placenta.

Treatment is briefly considered.

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SPECIAL ARTICLE

CHANGING PATTERNS OF MEDICAL PRACTICE*

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THE recognition of the importance of emotional stress in the genesis of certain disorders has been a fruitful concept so far as it has promoted the treatment of the patient as a whole. But if it is uncritically applied it may stifle the scientific investigation of disease mechanisms either as the result of attributing etiologic responsibility to the emotional accompaniment of any serious disorder or as the result of assuming that clinical entities of unknown etiology must be psychogenic in origin. The psychiatrically oriented physician is usually involved in a restricted type of practice, which furnishes no representative sample for gauging the frequency of psychosomatic disorders. The family doctor, whether he is an internist or a general practitioner, is often regarded as so psychiatrically obtuse as to be astonished when the emotional components of illness are pointed out. Perhaps his somewhat inarticulate attitude stems from his very consternation at the infinite and awful complexity of his patients' emotional problems and from his painfully acquired suspicion that awareness of psychic stress gives no assurance that it can be eliminated.

It seemed of interest, therefore, to study the type of clinical entity encountered in a random sample from an internist doing largely a family practice not devoted to any subspecialty. It was hoped that some estimate might be formed of the incidence of emotionally engendered illness today and, by comparison with a corresponding sample from the same practice twenty years ago, to evaluate the current claims that psychosomatic illness has shown an alarming increase. Is there statistical evidence to support Schindler's[1] statement that "emotionally induced illness comprises the bulk of medical practice"? Must one agree with Rennie[2] that "The psychoneuroses constitute the bulk of every general medical practice. By conservative estimate 60% of all the patients who go to private physicians suffer, not from organic disease, but from psychoneurotic conditions"? The estimate of Strecker et al.[3] "that as much as 40 or 50% of those coming to the general practitioner's office have a psychoneurosis as the major cause for the seeking of treatment" is more conservative but seems to need documentation.

TABLE 1. *Distribution According to Sex and Age.*

Group	Male Patients		Female Patients		Patients 0-10 Yr. of Age		Patients 10-20 Yr. of Age		Patients 20-30 Yr. of Age		Patients 30-40 Yr. of Age		Patients 40-50 Yr. of Age		Patients 50-60 Yr. of Age		Patients over 60 Yr. of Age		Totals	Averages
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage		%
1935	254	44	321	56	71	12	57	10	80	14	80	14	97	17	70	12	120	21	575	100
1955	588	44	744	56	101	8	147	11	121	9	138	10	214	16	248	19	363	27	1332	100

The current study is open to several valid criticisms even if basic statistical principles are rigidly followed to ensure proper sampling. My lack of formal psychiatric training cannot, perhaps, be offset by my intimate knowledge of the background of the patient and by my poignant awareness of the role of emotion

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in disease. And though this lack would furnish the same imperfect frame of reference for the study of the twenty-year-old sample, it might be argued that more cases of psychosomatic illness would be overlooked in that era because these concepts were then less aggressively popularized. Notations on the records of the older sample, however, suggest that I was no less aware of the role of emotion in disease twenty years ago than I am today. In the analysis of the two groups of records great care was exercised in differentiating between psychic or emotional stress that was of etiologic importance and that which was merely an accompaniment or product of the disorder. Now that each month in the year is dedicated by press and radio to the morbid contemplation of some dread disease, it is not surprising that many trivial ailments have acquired an emotional overlay that may be largely responsible for the incapacitating effect of the actual symptoms. Unless this emotional component of disease is clearly differentiated from emotional or psychic stress actually contributing to the genesis of the disorder, it is easy to conclude that emotionally engendered disease is on the increase. In this analysis various entities of unknown etiology such as peptic ulcer, rheumatoid arthritis and "essential" hypertension were not arbitrarily classified as psychosomatic, merely because of the current popularity of this concept, unless evidence of such stress could be elicited in a given case.

TABLE 2. *Diagnosis by Systems.*

SYSTEM	1935		1955	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
1. Cardiovascular	48	8	96	7
2. Respiratory	133	23	293	22
3. Digestive	70	12	175	13
4. Urogenital	27	5	78	6
5. Nervous	96	17	169	13
6. Endocrine	13	2	42	3
7. Musculoskeletal	59	10	145	11
8. Integumentary	95	17	161	12
9. Hematopoietic	13	2	19	1
10. (Physical examinations & immunizations of healthy patients)	21	4	154	12
Totals	575		1332	
Averages		100		100

MATERIAL

The study consisted of 575 consecutive patient visits spanning the four seasons in 1935 and a similar consecutive series of 1332 cases in 1955. Repeated visits for the same illness were not included in the analysis, but a patient seen for a different disorder was listed as a new diagnosis. Only 5 patients in the 1935 group reappeared in the 1955 series. The 1935 group was chosen from a period some years after I had begun practice to make it more comparable to the current group since the first year or two of practice is likely to have a disproportionately high incidence of seriously ill emergency patients and neurotic "medical tourists." The two samples were identical in sex ratio: 56 females to 44 males. Both samples included similar age groups, but the 1955 sample reflected the increased number of older people in the population and the fact that an older doctor attracts older patients. Fifty per cent of the 1935 sample, as compared to 62 per cent of the 1955 sample, were over forty years of age (Table 1). The diagnostic classification (Table 2) was patterned after the *Standard Nomenclature of Diseases and Operations* of the American Medical Association, with the addition of an entity to include healthy patients accepted for routine examination or for immunization.

TABLE 3. *Incidence of Organic Disease.*

CLASSIFICATION	1935		1955	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
A. Infection	185	32	381	28
B. Physical & chemical agents: Trauma & allergy	81	14	155	12
C. Disorders of metabolism: Diabetes, gout, avitaminosis, anemia & degenerative diseases	72	13	121	9
D. Neoplastic disease	15	3	23	2
Totals	353		680	
Averages		62*		51†

*Of 575 cases.
†Of 1332 cases.

RESULTS

As might be expected in New England, disorders of the respiratory system were the most frequent ailment, accounting for almost a quarter of the diagnoses in both the 1935 and 1955 series. Cardiovascular disease did not show the increase that might have been expected from the current furor on the subject and the greater age of the patients in the more recent sample. The frequency of disorders of the nervous system was due to the inclusion in this classification of neurasthenia, migraine and vascular headaches, neurocirculatory asthenia and cerebral arteriosclerosis. The relatively large number of ailments classified as disorders of the integumentary system reflected the inclusion of exanthemas as well as skin infections and superficial trauma. Some of these arbitrary attempts at simplification are open to obvious criticism, but they seem to be justified since the same criteria were applied to both the 1935 and

the 1955 group. Except for the recent threefold increase in patients requesting routine physical examinations and immunizations, it appears that they come to the doctor today for about the same disorders in about the same proportions as twenty years ago. To simplify comparisons, percentages in the tables are given in the nearest whole numbers. Tests of significance* were carried out with accurately calculated percentages.

A fourfold etiologic classification (Table 3) was attempted that would include only organic disease and from which any disorders of psychosomatic origin would be excluded. Infectious disorders need no explanation unless one is to become involved in speculation concerning the effect of emotion on susceptibility to infection. Disorders due to physical or chemical agents included trauma, involuntary intoxications and allergy when the specific allergen had been identified beyond reasonable doubt. Pollen hay fever and contact dermatitis were included. Angioneurotic edema, neurodermatitis and all asthmas were excluded because of their uncertain emotional component. Even the inclusion of trauma, with its implication of accident proneness, might be objected to by the psychiatrists on this account. Disorders of metabolism were admittedly a dumping ground and included gout, diabetes, avitaminosis, anemia and degenerative vascular disease. Malnutrition and obesity were not included because of the large emotional factors involved in both entities when food is available. Endocrine disorders were excluded, despite the metabolic implications of thyroid disease, because of the uncertain role of emotion in the genesis of some of them. The fourth group included benign and malignant neoplasms. If one assumes that all disorders not included in one of these four classes are psychosomatic one may test the validity of the previously quoted assumption[2] that 60 per cent of all patients who go to private physicians suffer, not from organic disease, but from psychoneurotic conditions. In the 1935 group 62 per cent of the patients suffered from organic disease. In 1955 this ratio had declined to 51 per cent, which is statistically significant although it is probably not clinically significant because of the threefold increase in healthy patients presenting themselves for immunizations or routine examinations. If this group (No. 10 in Table 2) is deleted from both the 1935 and 1955 series and the percentages of organic disease recalculated, it is found to have remained practically unchanged — that is, 59 per cent in 1935 and 58 per cent in 1955. However, even if one assumes that the remaining 49 per cent (comprising routine physical examinations and immunizations, arthritis, bursitis, peptic ulcer, fecal impaction, acute gastroenteritis of unknown etiology, impacted cerumen, spontaneous nosebleeds, endocrine disorders, skin disorders of unknown etiology and ill defined allergies) were of psychosomatic origin, the figure falls far short of the alleged 60 per cent.

The 1935 and 1955 groups were further analyzed for the incidence of serious illness. For this purpose a serious illness was defined as one whose symptoms would have been unbearable or whose effects would have threatened the patient's life or future health in the absence of treatment, as contrasted with a minor illness whose spontaneous recovery might safely have been awaited. The incidence of serious illness decreased from 14.3 per cent in 1935 to 12.2 per cent in 1955 but this is not statistically significant and

TABLE 4. *Distribution of Emotionally Engendered Disorders According to Sex and Age.*

GROUP	MALE PATIENTS		FEMALE PATIENTS		PATIENTS 0-10 YR. OF AGE		PATIENTS 10-20 YR. OF AGE		PATIENTS 20-30 YR. OF AGE		PATIENTS 30-40 YR. OF AGE		PATIENTS 40-50 YR. OF AGE		PATIENTS 50-60 YR. OF AGE		PATIENTS OVER 60 YR. OF AGE		TOTALS	AVERAGES
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE		
																				%
1935	25	26	73	74	1	1	8	8	22	23	26	27	14	14	16	16	11	11	98	100
1955	77	32	160	68	6	3	13	5	24	10	36	15	54	23	54	23	50	21	237	100

TABLE 5. *Emotionally Engendered Disorders — Diagnostic Distribution by Systems.*

SYSTEM	1935		1955	
	NO. OF CASES	PERCENTAGE	NO. OF CASES	PERCENTAGE
1. Cardiovascular	11	11	16	7
2. Respiratory	2	2	18	8
3. Digestive	22	23	59	25
4. Urogenital	1	1	8	3
5. Nervous	57	58	102	43
6. Endocrine	3	3	3	1
7. Musculoskeletal	2	2	24	10
8. Integumentary	0	0	7	3
9. Hematopoietic	0		0	
Totals	98*		237†	
Averages		100		100

*17% of 575 cases in 1935.
†18% of 1332 total cases in 1955.

*p=0.01 is a commonly accepted level of significance, meaning that differences as large as those observed could occur as the result of chance alone not more than once in a hundred samples of the size employed. This level of significance was employed in the current study.

cannot be interpreted as evidence of an increase in functional disorders.

Finally the two groups were compared for incidence of disorders in whose genesis psychic or emotional stress played a part (Tables 4 and 5). In 1935, 17 per cent of the disorders were in whole or in part emotionally engendered. This had risen by only 0.8 per cent in 1955, which is not significant. There was a higher rate of psychosomatic disorders among females in both the 1935 and the 1955 groups than could be explained by the over-all preponderance of females (56 per cent) in the entire series. The age distribution of the emotionally engendered disorders in 1955 showed a shift to the later decades comparable to that of the 1955 group as a whole. The classification of these disorders according to the systems involved (Table 5) suggests that the digestive and nervous systems bore the brunt of the stress in 1955 as they did twenty years ago. The actual number of cases in these diagnostic classes was too small to warrant any further conclusions.

Conclusions

Analysis of comparable random samples of cases twenty years apart in the same internist's practice fails to substantiate the current belief that emotionally engendered disorders have shown an alarming increase and now constitute more than 50 per cent of medical practice.

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MEDICAL PROGRESS

APNEA AND RESPIRATORY DISTRESS IN THE NEWBORN INFANT (Concluded)*

Physiologic Background, Resuscitation and Supportive Technics

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Tank-Type Respirator

Whether expanding forces are applied to the lungs via a face mask with positive pressure or by means of negative pressure applied to the chest (and abdomen), the physiologic effects are similar. Thus, the same factors that contribute to safe expansion are important in both, and such complications as gastrointestinal distention are seen with both procedures. In actual use, the practical limitations of prolonged application of either a face mask or a tank respirator are most important.

A tank or "iron-lung" respirator should, theoretically, be as useful as an electrophrenic respirator in the treatment of apnea, and even more useful in assisting inspiration of infants with distress. Although electrophrenic respiration is limited by the strength of the infant's muscles and thoracic cage, intrathoracic negative pressures of any desirable amount should be obtainable in an ideally designed and fitted tank or cuirass.

Rhythmically-cycled tank respirator. In tracing the development of "breathing machines," the Medical Research Council in England[104] mentioned the development of "a device . . . for resuscitating an asphyxiated newborn child" by Dr. Egon Braun, of Vienna, in 1889. This apparatus consisted of a box in which the infant was placed with his face protruding through the top while the pressure was changed within the box by means of a bellows. The respirator was exhibited to the Boston Medical Society in 1889, but does not appear to have had much clinical use. Since that time there have been sporadic attempts to treat the infant with respiratory difficulty with modifications of Braun's chamber. Wilson[105] attempted to use the Drinker respirator to ventilate the lungs of apneic premature newborn infants. His experience was not encouraging enough to warrant further efforts, although one effect noted was that movements of the neck collar that he employed seemed to stimulate the infant to take spontaneous breaths. Murphy and his co-workers[106,107] also worked with a Drinker type of respirator but could not obtain consistently satisfactory results.

Donald and Lord[108] state that their experience with this type of machine has been discouraging be-

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cause the baby fought the rhythm of the machine with its own variable respirations, if strong enough to do so, or promptly went into what they termed "protest apnea," after which some large breaths might or might not be forced in. They also suggested that alkalotic tetany might theoretically develop as a result of hyperventilation, and therefore considered limiting the use of this respirator to periods no longer than three minutes. However, no such overventilation has been reported, and it seems likely that the real threat to the infant needing resuscitation or assisted respiration is anoxia and probably also hypercapnea.

These considerations indicate that the machine was not being used by Donald and Lord primarily to overcome apnea but rather to provide mechanical assistance to infants capable of considerable (though inadequate) respiratory efforts of their own. In this concept of "assisted respiration" Donald has been one of the first to adapt technics used in adults to the infant with respiratory distress.

Patient-cycled tank respirator. Donald and Lord[108] have attempted to avoid the difficulties of rhythmically cycling tank pressures by means of a machine in which the infant's own inspiratory efforts initiate the assisting mechanism. This tank respirator responds instantaneously with negative pressures that may be regulated at between −15 and −30 cm. of water. Donald and Lord have selected patients for assisted breathing on the basis of clinical history, x-ray study of the chest, measurement of minute volume by means of a spirometer and an estimate of the work of breathing obtained from the ratio of tidal volume to intraesophageal pressure change. Although they state that "the disappointment-rate is very high," they have at least been able to demonstrate that spontaneous pulmonary ventilation can be increased with this type of patient-cycled respirator. Technical difficulties in the operation of the apparatus, especially in obtaining an adequate seal around the infant's neck or face, have accounted for some failures; other infants have succumbed to such complications as intraventricular hemorrhage. Nevertheless, the principle of assisted respiration appears to be an important one in the treatment of infants with respiratory distress. If this device, or some modification, can be shown to be effective and practical when used by other workers, it may successfully aid some of the infants who would otherwise die of respiratory-muscle exhaustion before their pulmonary insufficiency begins to improve spontaneously.

Air lock. The Bloxsom air lock[109] is essentially an incubator in which the pressure is rhythmically varied between 1.0 and 3.0 pounds per square inch (52 to 156 mm. of mercury) above atmospheric pressure. The pressure is raised in approximately 45 seconds and reduced in 7 so that a complete cycle requires almost 1 minute. The apparatus has been used in a variety of clinical situations ranging from "depressed" newborn infants to those thought to have the "hyaline-membrane syndrome."[110,111] Lacking any better critical measurements, Townsend[110] has attempted to compare the appearance of 150 infants in the apparatus with and without cycling. It may be significant that 49 infants were apparently improved by the cycling, but it is unfortunate that there is no report of an alternate case study of the effect of this device on morbidity or mortality in an adequate number of newborn infants. If the air lock does have a beneficial effect, the question of its mechanism arises. From the experimental work of Apgar and Kreiselman[112] on apneic and hypoventilating dogs, and from comments by Wilson, Smith, Barach and Whittenberger on a report by Bloxsom,[113] there is little or no reason to expect the apparatus to inflate unexpanded lungs, to provide more than a fifteenth of the oxygen requirement by diffusion of oxygen through the skin or to produce an effective exsufflation whereby secretions could be eliminated from the airway. Townsend[114] has suggested that the benefits are related to differences in airflow resistance in different portions of the pulmonary air passages. However, at present, there are no physiologic data available to support such a hypothesis.

Gravity Technics

Various rocking technics have been used to maintain adequate pulmonary ventilation in laboratory animals, older children and adults.[115-119] These have also been used in apneic or hypopneic infants and infants with later respiratory distress,[120-126] but unfortunately no measurements of air exchange thus produced have been reported. Studying adults and children, Ferris[127] found a direct correlation between abdominal length and effectiveness of rocking technics. On the basis of this work and further studies with a model chest-diaphragm-abdomen preparation, it seems theoretically unlikely that a newborn infant could derive any significant pulmonary ventilation from the effect of gravity on subdiaphragmatic contents. The presently available rocking beds for infants also share the disadvantage of many of the other instruments already discussed, in that they cycle rhythmically without relation to the infant's own respiratory effort.

A number of uncontrolled observations on the use of the rocking technic have been reported. The earliest of them was described by Forsyth,[128] who rocked a pallid, apneic newborn infant in his arms until breathing began spontaneously after 50 minutes of 15 cycles to the minute. He reported audible air movement after the first minute of rocking. The later experience of Eve and Forsyth[120] included 11 cases of asphyxia pallida, with no deaths. Rocking was not attempted on those with "cerebral hemorrhage"; the criteria for this immediate diagnosis of cerebral bleeding were not mentioned.

With rocking as their only resuscitative technic, Millen and his co-workers[128] were unable to attribute any neonatal deaths in a series of 4000 consecutive

deliveries of infants of over thirty weeks' gestation to failure of initiation of respiration. In another study, Handley and Handley[121] rocked all apneic infants (50 cases) in whom there was evidence of pulsation of the cord or a perceptible heart beat. The duration of apnea before rocking was not stated. None of these infants failed to revive, although 1 later died with cerebral hemorrhage.

In contrast to these favorable reports, Pedvis, Irwin and Philpott[124] were unable to show a significant change in survival rate of babies delivered by cesarean section after adoption of postural drainage and rocking when indicated. Even the proponents of the rocking technic prescribe supplementary resuscitative measures. Roberts[125] describes and uses a rocking bed, but also administers oxygen endotracheally when required. Eve and Forsyth,[120] who originally used the rocking method in adults, recommended that the rocking of newborn infants should be preceded by attempts at mouth-to-mouth inflation of the lungs.

It has been suggested that at least part of the benefit to be derived from rocking is based on the improvement in the circulation.[117,119,120,123] At present no quantitative hemodynamic measurements to substantiate this hypothesis are available. Finally, although there is no critical evidence concerning the value of the rocking technic, it seems reasonable to say that this procedure is safe and may prove to have some benefit for small, premature or narcotized infants who occasionally stop breathing and require some nonspecific mechanical stimulus to prod them into respiratory movement. Also, the device may be shown to have some benefit during the first three or four days of life, when fatigue becomes a factor.[122]

Manual Resuscitation

Attempts at manual resuscitation by compression of the infant's thorax or abdomen are frequently resorted to in the apneic infant. This is a futile procedure if the lungs contain no air and is dangerous, for rib fractures are easily produced. Other resuscitative procedures for the apneic infant should therefore replace this technic.

Artificial Hypothermia

Increased tolerance to lowered body temperature and an extraordinary resistance to anoxia have been well established in neonatal animals, particularly the less mature.[8,129,131] Adolph[129] suggests that these two phenomena are unrelated since the resistance to anoxia is lost before the tolerance to cold. Nevertheless, Himwich and Fazekas[8] attribute the prolonged survival of fetuses or neonatal animals during oxygen deprivation to poikilothermia as well as to the capacity to generate a relatively increased amount of energy via anaerobic pathways.

The usefulness of hypothermic technics in cardiac surgery has elicited much investigation concerning the fundamental processes. It has led, also, to attempts to apply hypothermia to the prevention of anoxic damage in newborn infants on the supposition that ventilatory balance might be improved by reduction of oxygen consumption and carbon dioxide production.[132-134] However, hypothermia would only be beneficial if the oxygen need and carbon dioxide production were reduced to a greater extent than the alveolar ventilation. Hypoventilation and then respiratory arrest occur in laboratory animals, older children and adults in hypothermia of the degree used in cardiac surgery.[135,136] Levels of hypothermia suggested for newborn infants, however, are not as extreme as those used for surgical purposes. Unfortunately, no critical data concerning the physiologic effects of mild to moderate hypothermia in the newborn period are yet available. Hypothermia does not seem to have any place in the treatment of initial apnea, because, although it might decrease oxygen consumption, it would almost assuredly also decrease respiratory-center responsiveness.

Karlberg[133] has suggested that, in his adjustment to pulmonary insufficiency, an infant reaches his limit of adaptation when the respiratory rate rises to 100 to 120 per minute. He has lowered the incubator temperature until the respiratory rate dropped to somewhere between this limit and the normal. Body temperatures (by rectum) of approximately 91°F. were reported. Apparent clinical improvement in a few cases of severe respiratory distress in the newborn infant occurred. Holmdahl[132] uses "hibernation" prophylactically for premature and term infants whose history suggests a predilection to "asphyxia" — for example, post-maturity, a diabetic mother, complicated delivery, cesarean section, evidence of intra-uterine asphyxia and breech presentation. Unfortunately, no results are yet reported.

Lacomme and his co-workers[134] describe a series of infants to whom chlorpromazine was administered to maintain the body temperature at 93 to 94°F. It was injected subcutaneously every forty minutes for twenty-four to thirty-six hours. From a total of about 4400 births, 60 full-term and premature infants were selected for treatment, and in this group there were 40 deaths. Lacomme et al. report clinical improvement consisting of decreased cyanosis and a change from shallow, periodic respiration to deep, regular patterns. Although these authors apply the term "life-saving hibernation" to some of their experiences, the data presented are not sufficiently critical for analysis. Furthermore, the temperature did not fall as low as the body temperatures observed, at times, in apparently normal and premature newborn infants.[137] The fact that, as usually measured, the rectal temperature, particularly in the premature infant, is not a reliable index of body temperature[138,139] creates another source of difficulty in evaluating the reports. Finally, it seems that the possible usefulness of mild hypothermia in the newborn period is rational only in the treatment of peripheral pulmonary insufficiency; its actual efficacy remains to be established by critical physiologic measurements.

Aerosols

Various nebulized or aerosolized liquids have been successfully employed in the reduction of obstruction from tenacious mucus in the upper air passages. Although respiratory distress of the newborn infant appears to be primarily due to peripheral disease, aerosolized agents have been utilized in attempts to ease or prevent the difficult breathing of neonatal respiratory distress.

Mist. The use of atmospheres supersaturated with water in neonatal respiratory distress presupposes that water particles will penetrate to the smaller air passages and, once there, will have some beneficial effect on lung expansion or gas diffusion or both. Unfortunately, no critical data are available on either of these points. However, the humidity of alveolar air is approximately 100 per cent in adults; if this pertains in the newborn infant with respiratory distress, the value of attempts to increase this still further can be questioned.

The only controlled study reported to date is one by Silverman and Andersen,[140] who found no beneficial effect on respiratory symptoms, death rate or autopsy findings in a group of 103 premature infants treated with mist compared to a control group of 97 premature infants cared for in 90 to 100 per cent relative humidity. The results of this study indicate that the routine use of mist in premature infants with or without respiratory distress does not seem warranted. Furthermore, a suggestive increase in the frequency of *Pseudomonas aeruginosa*[141] and monilial infections in infants placed in mist needs additional consideration.

Wetting agents. Clinical reports on the successful use of wetting agents in the treatment of respiratory distress of newborn infants have been numerous. It is unfortunate that, on the basis of inadequate data, one agent has been publicized as being particularly effective.[142] The recent controlled study carried out on a total of 200 premature infants by Silverman and Andersen[143] failed to show any therapeutic benefit, as judged by death rate and autopsy findings, that could be credited to Alevaire mist therapy. The only other controlled study is that of Briggs[144] on 62 newborn infants who had respiratory distress. He also concluded that the wetting agent, Alevaire, with oxygen was no better than oxygen and high humidity in promoting pulmonary expansion. These two studies furnish evidence that this wetting agent is of no significant therapeutic help under the conditions specified.

Enzymes. Aerosolized enzymes such as trypsin have been used in the therapy of neonatal respiratory distress, but no evidence of benefit is available. If hyaline membranes are actually of clinical importance, enzyme therapy could theoretically be of value. However, in practice, it seems likely that concentrations in the air reaching the alveolar ducts and alveoli are too dilute and are present for too short periods to be of practical importance; larger concentrations would probably produce tissue damage to the lung as they do in certain other parts of the body.[145]

Gastric Suction

Most of the resuscitative technics and devices thus far reviewed have been primarily applicable to the therapy of respiratory failure. So little is understood of the pathogenesis of peripheral difficulty in the newborn infant that few methods for prevention have even been proposed.

In 1949 Gellis, White and Pfeffer[146] reported their experiences with gastric suction in preventing or reducing subsequent respiratory distress in infants of diabetic mothers delivered by cesarean section. They suggested that the respiratory difficulty frequently occurring at or shortly after birth in these infants and sometimes present in nondiabetic infants delivered by cesarean section might occur if an excessive amount of gastric fluid were regurgitated and aspirated. From 25 such infants delivered by section the authors were able to remove an average of 21 ml. of gastric fluid; 4 had respiratory distress at birth, but no additional infants had difficulty later. Of 25 control infants, not aspirated, 6 had initial respiratory difficulty, and 9 additional infants showed subsequent respiratory abnormalities. Gellis et al. pointed out that this series was too small to be valid statistically and that there were many variables that made comparison of their two groups impossible. Nevertheless, they concluded that gastric suction had a significant beneficial effect.

Subsequent workers have been unable to aspirate as much fluid. Little and his co-workers[147] obtained an average of 6.4 ml. of gastric contents from cesarean-section infants, compared with 5.2 ml. from 50 infants delivered normally. The subsequent effect on respiratory distress was not evaluated. The over-all corrected mortality rate of 4.4 per cent for 225 babies delivered by cesarean section during a control year was compared to one of 2.8 per cent in the 179 infants treated by gastric aspiration. The significance of this difference is limited by many uncontrolled variables.

Freeman and Scott[148] obtained an average of 6.2 ml. of gastric contents from cesarean-section infants, as compared with 3.6 ml. from normally delivered controls — a difference that seems unlikely to be significant to the infant. The group treated with gastric aspiration was considered to show less respiratory distress than a control group, but the criteria for "distress" were not defined in the paper.

Conclusions concerning the value of removal of gastric contents have been based primarily on clinical impressions, without x-ray or autopsy proof that pulmonary aspiration of gastric contents actually occurs before the onset of respiratory distress or is reduced by this procedure. What effect the excessive crying, caused by repeated gastric aspirations, would have on pulmonary expansion remains unanswered. Moreover, the origin of the excessive gastric contents of infants of diabetic mothers remains unknown. Thus,

the reports available do not establish the need for routine gastric suction in cesarean-section deliveries. Obviously, gastric suction, if performed carefully and with low negative pressures (5 cm. of water), is a safe procedure and effectively rules out esophageal atresia.

Surgical Procedures

The marked sternal retraction exhibited by newborn infants with peripheral respiratory distress has suggested to a number of workers that therapy should be directed toward fixation of this portion of the chest. It has been reported[149,150] that mechanical traction on the sternum produces more efficient respiration in the few infants so treated. However, no critical supporting data are available. Certainly, abnormalities of the thoracic cage are not the cause of sternal depression but rather the greatly increased intrathoracic negative pressures necessitated by the high elastic resistance of the lungs (Table 2). If fixation of the sternum increased the mechanical efficiency of the respiratory muscles or even increased functional residual volume, it might well be a useful procedure. Studies in this hospital showed that, at least in 1 infant, sternal traction had no effect on mechanical efficiency of the respiratory muscles; presumably, this infant, like most of those who are critically ill, was making a maximal respiratory effort with or without sternal traction. Further attempts to make exact measurement of the effects of this procedure are probably indicated, but at present, with little supporting data or theory, the technic can only be considered experimental.

Thoracotomy and expansion of the atelectatic lung under direct vision is a procedure that has been used in a number of infants.[151] Although it is thus possible to expand the lung without expanding the chest, the results do not appear to justify such a drastic and potentially dangerous procedure.

Discussion

As in almost all fields of clinical medicine, prevention of abnormal states should be the primary object of medical care. The fact that resuscitation of the initially apneic infant has become a relatively infrequent procedure in the Boston Lying-in and many other hospitals indicates that through better obstetric and anesthetic management of parturient women much progress has already been made. Any hospital with a significant number (more than 1 or 2 per 1000 live births) of infants dying who might be considered potential or actual problems in resuscitation should re-examine its program of general care of the pregnant woman rather than invest in new resuscitating devices. However, in the occasional infant who under the best of circumstances requires resuscitation, some safe program should be available. The one currently in use at the Boston Lying-in Hospital is as follows[152]:

When possible, central-nervous-system depression should be prevented or reduced by avoidance of trauma, intra-uterine anoxia, drugs and excessive anesthesia. Oxygen should be administered to the mother during delivery when fetal distress is suspected because of the passage of meconium or a significant elevation or depression of the fetal heart rate.

An airway should be quickly established and maintained.* The infant should be suspended on the operator's forearm, head down, with the neck extended to straighten the trachea. The trachea is gently milked toward the mouth. The mouth, pharynx and nose are aspirated with a soft, sterile catheter or rubber aspiration bulb. If mouth suction is used, a trap must be present to preserve catheter sterility and catch material from the infant's respiratory passages.

Spanking and rubbing are not as safe as the simple sensory stimuli resulting from birth.

Oxygen may be given by funnel or mask, or the infant may be placed in an oxygen tent or incubator.

If reasonably adequate breathing does not begin, a Kreiselman machine is used to oxygenate the lungs, blood and brain by safe positive pressures through a small mask. The pressures used are approximately 22 cm. of water for the first 10 puffs at five-second intervals and then 20 cm. of water for puffs repeated over a longer period — up to fifteen minutes. The purpose of its use is not to "blow up" the lungs visibly, but to improve the infant's color and tone.

The infant is kept slanted head downward.

Body warmth is maintained by blankets or an incubator.

On the infant's chart the time before the first respiration and cry is recorded as accurately as possible.

One should, above all, avoid procedures that might do harm.

This program is obviously based on the premise that most infants need, if any, only brief assistance in resuscitating themselves, rather than more dynamic attempts to substitute artificial ventilation for their own efforts. Oppé[153] found that in approximately 4500 deliveries at the Boston Lying-in Hospital in 1943, 14 infants whose hearts were beating at birth failed to survive the first four hours thereafter. Ten years later, in 1953, of approximately 5500 comparable deliveries, only 6 infants succumbed within four hours and could be considered as possible failures of resuscitation. Thus, although important in the individual case, initial resuscitation of the newborn infant should, in general, be an infrequent problem.

Because of this infrequency and many uncontrollable factors the treatment of apnea of the newborn is particularly difficult to assess. Carefully controlled

*Oral airways and, in rare cases, endotracheal tubes might supplement these steps.

alternate case studies are understandably difficult to carry out. No data thus obtained are available for many technics so that some are being used that may well be useless and even harmful. Comparison of the efficacy of various technics of resuscitation requires some means of evaluating the severity of anoxia and central-nervous-system depression exhibited by infants reported by different authors. Such a system of classification of neonatal asphyxia has been suggested by Apgar[154] (Table 3) and has been used for the classification of approximately some 10,000 newborn infants. Not until some such grading of newborn infants becomes standard will comparisons of results of resuscitation reported by various clinics using differing technics be possible.

TABLE 3. *Evaluation of the Newborn Infant One Minute after Birth.**

Score†	Heart Rate	Respiratory Effort	Reflex Irritability	Muscle Tone	Color
2	100-140	Normal cry	Normal	Good	Pink
1	<100	Irregular & shallow	Moderately depressed	Fair	Fair
0	No beat obtained	Apnea for more than 60 sec.	Absent	Flaccid	Cyanotic

*Based on data of Apgar.[154]

†Each type of observation scored as indicated. Total scores: 8-10, good; 3-7, fair; 0-2, poor condition.

In contrast to the relative infrequency of initial apnea of the newborn as a cause of death, progressive respiratory distress contributes most significantly to neonatal mortality (15 to 20 per cent of the infants with respiratory distress die,[155] and this condition accounts for 40 to 50 per cent of all neonatal deaths).[156] However, in the area of prevention and treatment of this type of respiratory difficulty, few, if any, clinically applicable technics have been proved to be effective. One can only state that respiratory distress, when it occurs, is usually associated with prematurity, maternal diabetes and intra-uterine distress, especially when these lead to cesarean section. Some of these conditions can be avoided or controlled, and by this means some cases of neonatal respiratory distress are presumably avoided. But, at present, practical means of prevention of the majority of cases of respiratory distress are not available. The possibility that some cardiovascular-pulmonary imbalance before, during or after birth is etiologically related to later respiratory distress has been mentioned and may prove a fruitful area of research. Possibly, venesection, digitalization, early positive-pressure breathing to improve initial expansion or some method of changing the timing of postnatal circulatory readjustments may be useful approaches in the future. But, whatever prophylactic method is employed, it should be safe, for it must be applied to many normal infants to include all those in whom respiratory distress might develop. Gastric aspiration is reportedly a prophylactic technic but at best it can only be said that many cases of respiratory distress occur in spite of the most enthusiastic use of this method. Hypothermia, although used for this purpose, does not seem to be a rational prophylactic device.

Just as very little is known about the prevention of neonatal respiratory distress, there is scant knowledge concerning its treatment. A hopeful feature is the apparent self-limitation of the process. The most significant abnormality appears to be some unknown intrapulmonary factor that interferes with the oxygen uptake and carbon dioxide removal and at the same time makes the lung very resistant to expansion. It is apparent that these handicaps are associated with an increased physiologic dead space and a very significant increase in the work of respiration. At present, the great need is for some means of reversing the basic process. Until such specific therapy is available, useful supportive measures must be sought. Oxygen therapy will partially alleviate the anoxia that frequently accompanies this condition. However, only some form of "assisted respiration" can aid in carbon dioxide removal by actually increasing alveolar ventilation and supplementing the infant's own strenuous respiratory efforts. Practical devices, whether of the positive-pressure or tank type, are needed in this area and when available must be carefully evaluated. At best, it seems apparent at present that the success of such devices will depend on interested and skilled personnel; the apparatus seem so necessarily complex as to preclude general use. If a device, however complicated, became available, the group of fetuses with the greatest risk of respiratory distress might be selected before delivery and cared for in appropriate centers.

Finally, the very obvious difficulties inherent in supportive treatment emphasize the great need for researches that will eventually lead to an understanding of the basic processes, a practical means of prevention and a specific form of therapy. In this Medical Progress report the discussion of progressive respiratory distress has been primarily limited to a clinical condition of unknown etiology. It must be remembered that by no means all respiratory distress in the newborn period is of this type. Every effort, including a careful history and physical examination, esophageal catheterization, roentgenographic studies and cultures, should be made to arrive at specific diagnoses, especially when specific therapy is applicable.

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MEDICAL INTELLIGENCE

PERFORATED DUODENAL ULCER COMPLICATING PREDNISONE THERAPY*

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OUT of a group of 18 arthritic patients treated with prednisone (Meticorten) we have encountered 3 with peptic ulcers; 1 of these, in whom a perforation developed, is the subject of this report.

Peptic ulcer as a complication of prednisone therapy has previously been reported,[1] as has 1 case of massive hematemesis from peptic ulcer in a patient with the nephrotic syndrome treated with prednisone.[1,2] Bollet et al.[1] have also noted the healing of peptic ulcers in 2 patients on a rigid ulcer regimen without reduction in prednisone dosage. There has not been, to our knowledge, a previously published report of perforated ulcer in a patient on prednisone therapy, but it is certain that other cases have occurred.[3]

CASE REPORT

A 21-year-old married woman was first seen at Harper Hospital in August, 1952, and subsequently hospitalized 5 times. At the 1st admission she was thought to have infectious arthritis (associated with pelvic inflammatory disease), and on the 2d the symptoms resembled those of rheumatic fever. On the 3d admission, in January, 1953, the diagnosis of rheumatoid arthritis was well established by clinical, laboratory and x-ray findings.

Varying combinations of cortisone, ACTHAR Gel, intra-articular injection of hydrocortisone, antibiotics, salicylates and phenylbutazone were employed, with unimpressive results. On discharge from the hospital on February 11, 1955 (the 5th hospital admission), the patient was instructed to take daily 30 units of ACTHAR Gel intramuscularly and potassium chloride orally along with other supportive meas-

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ures, including physical therapy. Gold therapy was started on March 4 (25 mg. of Myochrysine weekly). Three weeks later gratifying improvement was noted, and the dosage of ACTHAR Gel was gradually reduced over the next 2 weeks to 5 units daily. However, after this reduction, joint pain increased, and the wrists and knees became swollen and tender, with movement markedly restricted.

On April 15 the ACTHAR Gel was discontinued (as was Myochrysine) and prednisone, 5 mg. 4 times daily, was started. The pain, swelling and tenderness of the knees and wrists decreased appreciably after 1 week, and the dosage was increased to 5 mg. 5 times daily. However, because of slight edema of the ankles and feet, it was again decreased to 5 mg. 4 times daily at the end of 2 weeks. The patient was quite comfortable during the next 2 months; the edema had subsided without salt restriction, and slight facial rounding had developed.

On July 21 she was admitted to the hospital as an emergency case because of abdominal pain of 3 days' duration. Twenty-four hours after onset the pain had localized in the epigastrium and could be relieved temporarily with aspirin and codeine, but not by food. In the 12 hours before admission it had shifted to the right upper quadrant of the abdomen, had become more severe and was accompanied by nausea and vomiting. She reported having had epigastric pain in the morning for a 7-day period 1 month before admission. This was readily relieved by milk so that she did not report the incident.

Physical examination showed a woman in acute distress, lying on her back with the knees and hips flexed. There was tenderness on the right side of the abdomen that was maximal in the right upper quadrant. The rebound phenomenon was present, and there was generalized muscular rigidity. Bowel sounds were active. Moderately tender fusiform swelling of both knees was noted, and the wrists were in volar flexion, with early flexion deformity.

The temperature was 100.6°F., and the pulse 92.

The white-cell count was 12,000, with 83 per cent neutrophils and 14 per cent lymphocytes, and the hemoglobin 11.8 gm. per 100 ml. Twelve hours later the abdominal tenderness and the pain had become more severe. The white-cell count was 11,300, with 72 per cent neutrophils and 24 per cent lymphocytes. A ruptured viscus was suspected, and the patient was prepared for laparotomy.

On exploration, a perforation 3 mm. in diameter was found in the anterior wall of the 1st portion of the duodenum. This was closed without difficulty. Steroid therapy before, during and after operation consisted largely of intravenous and intramuscular administration of hydrocortisone, with gradual reduction in the dosage postoperatively. Recovery was uneventful, and the patient was discharged on the 12th postoperative day.

She was placed on a rigid ulcer regimen and fared well for the 1st 3 weeks after discharge. Then the rheumatoid disease was reactivated, with poor response to the measures instituted for relief. Eight weeks after the perforation x-ray studies showed healing of the ulcer.

Discussion

Prednisone has been widely accepted for the management of severe rheumatoid arthritis because it is more effective, there is less electrolyte disturbance and, at least in the early reports, few significant complications were reported.[4-6] These advantages have seemed even greater as the diminishing returns and undesirable effects of long-term therapy with cortisone, hydrocortisone and ACTH have been recorded.[7-9] However, it has been observed that gastrointestinal complications may develop during the administration of prednisone. The need for caution during its use is indicated by Bunim's[3] knowledge of 4 perforations of an abdominal viscus, — 3 cases of peptic ulcer (2 gastric) and 1 diverticulum of the sigmoid — and our experience with the case described above, as well as the finding of peptic ulcers in 2 other patients out of a group of 18 patients with rheumatoid arthritis treated with prednisone.[1,10]

It is too early to know whether gastrointestinal complications can be prevented, but the experience of Bollet et al.[1] suggests that they can if proper precautionary measures (such as x-ray studies of the upper gastrointestinal tract and an ulcer regimen) are taken. Sandweiss[11] considers it unnecessary to withhold steroid therapy (when it is definitely indicated) because of fear of peptic ulcer, which can probably be partially, if not completely, prevented by ulcer regimens and, even more important, by adequate preliminary search for an ulcer. We believe that such a preliminary study is indicated in all patients in whom long-term steroid therapy is contemplated.

Conclusions

A perforated duodenal ulcer developing in a patient on prednisone therapy for rheumatoid arthritis, and the finding of ulcers in 2 other patients in a group of 18 under similar treatment indicate the need for an adequate search for peptic ulcer before such therapy is instituted. It is suggested that, with adequate precautions, it is unnecessary to withhold this steroid because of fear of peptic ulcer.

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DOCTORS AFIELD

C. A. Stephens (1844-1931) — Popular Author and Prophet of Gerontology

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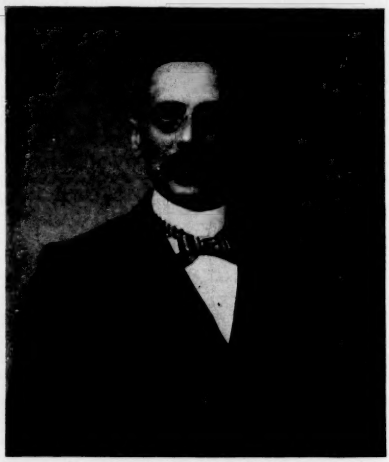
QUITE a few doctors are old enough to remember when C. A. Stephens was one of the best-known and most-loved American authors. But few

indeed know that the popular writer for the *Youth's Companion* was a physician himself and a scientific thinker of great originality.

Charles Asbury Stephens was born near Norway, Maine, on October 21, 1844.[1-3] He was the only child of a devout Methodist couple. Both his parents came from vigorous and successful farming families, and his great-grandfather, a hardy pioneer, had been the first settler in the Norway area.

Stephens grew up in the years before the Civil War when rural areas were still quite isolated from intellectual and cultural activities. But he was a sensitive and keenly observant boy, and, lacking scholarly diversions, he studied the life around him till its features were indelibly etched in his mind. He responded to the beauty of his environment — to the west the Presidential Range of the White Mountains edged the sky, and to the south Lake Pennesseewassee glittered in a setting of wooded hills that is now a tourist area. He noted the homely features of life on the farm and in the village, and, years later, a vast audience responded to the absolute authenticity of his perceptions. Stephens also saw and stored in his memory the less pleasant phenomena of the society of his day — the ravages of superstition, the cruel treatment of the aged and the insane and, above all, the ever-present tragedy of death.



His career in academy and college was a constant struggle against financial anxiety. He peddled sewing machines, chopped wood and taught school and finally was able to complete his courses at Bowdoin College in 1869.

While at Bowdoin, he had won the essay-writing prize in his class, and he decided to market his talent. At first he tried to sell serious articles on scientific subjects.[4] He was much more fortunate when he submitted short stories directed to children and teenagers and based on his own reminiscences; he won the patronage of Daniel F. Ford, enterprising publisher of the weekly periodical *Youth's Companion*.

In 1870 Stephens and Ford worked out an unwritten contract that began one of the most phenomenally successful ventures in the history of American journalism.[5] Stephens at times wrote large sections of the periodical, signing some articles with assumed names and leaving others unsigned.[6] His work was in that border area that appeals to youngster and adult alike. His style was simple and direct: the plot was developed gradually and often with gentle humor, and the setting was completely realistic. He traveled to every part of the United States and to Alaska, Panama, the West Indies, Mexico and Europe in search of material. Meanwhile, Ford devised ingenious promotional technics featuring attractive premiums for subscription hunters. By 1885 the circulation of *Youth's Companion* had reached 385,000. It was the most popular periodical in America.[7]

Daniel Ford's ambition was not mere money making.[8] He wanted to uplift and educate the people — the Ford Hall Forum in Boston is his legacy. Among other things, he wanted a weekly health column in the *Youth's Companion*. In 1884 C. A. Stephens volunteered for the job, and Ford paid his way through Boston University School of Medicine. Stephens took the three-year course, continuing his journalistic duties at the same time, and graduated in 1887 with excellent grades.

Many years before, while still a child, he had clipped out a quotation from Alexander Hamilton, "All the genius I have lies just in this: when I have a subject in hand, I study it profoundly . . . My mind becomes pervaded with it." Ford did not know it, but C. A. Stephens had "a subject in hand." It was not journalism or even public health. It was the ancient and baffling problem of death.

Writing of his childhood, Stephens once recalled the impact of the first funeral he had ever seen,

> . . . I should have to die and look as that man looked and be buried in the ground. The thought of it caused me to gasp suddenly, and filled me with a sense of terror and despair so awful that I could scarcely restrain myself from crying out. Most young people, I conjecture, pass through a similar mental experience, when the dread fact of death is first realized.[9]

Since that time, he had done much thinking about death. After graduation from medical school he continued his work for the *Youth's Companion*, but all his spare time was devoted to study and research on old age and death. He read everything he could find on aging processes. He obtained dogs in 1890 from the New York pound and compared slides of the

brain tissue of old dogs and young dogs.[10] He offered a prize of $175 for the best microscopical demonstration of the capillaries in tissue taken from young and from aged animals.[11]

His greatest desire was to establish a grandiose international organization to promote "researches into the causes of disease, old age and death."[12] He also hoped to expand his laboratory into an institute of gerontology.[13] On the basis of rather vague assurances from a wealthy friend he built a large and rambling wooden structure capable of housing fifty scientific workers, but the friend died suddenly in 1905, and the heirs were not interested in the project.

Stephens published at his own expense at least eleven books dealing with his scientific study and philosophical speculation. They are of uneven quality, as one might expect from a person with his volatile enthusiasm and his distrust of academic authority. The earlier works, however, are in general quite abreast of the science and philosophy of the day; the later ones are not. After 1907 he became more and more entangled in health-cult ideas.

The basic thought in Stephens's philosophy is what may be called the idea of prolongevity — the belief that science may someday be able to extend greatly the length of human life. The concept has had a long history in American thought.[14] Benjamin Franklin was one of the first Americans to express the idea,[15] and since then it has continued as a variant of one of the most powerful currents in American intellectual history: the belief in progress.

Stephens grew up at a time when faith in progress was reaching its greatest strength in America.[16] His most cogent philosophical work, a small book called *Natural Salvation* (1903), is a zealous but obviously sincere synthesis of the utopian ideas of the eighteenth-century enlightenment fused with Darwin's theory of evolution and focused on the problems of old age and death. According to Stephens, if society were to direct its resources into scientific research the investment would be lavishly repaid: the conquest of disease and senility would make immortality itself possible. This doctrine he called *natural* (or scientific) salvation.

It is difficult to evaluate the significance of C. A. Stephens at this time. His literary reputation is reaching a low ebb as the generation that admired him grows older and less numerous. An eminent Boston man of letters has commented on Stephens's work as follows:

> He thought the thoughts and spoke the language of a vast body of Americans throughout the country, and was, I believe, unique among writers in the possession of unquestionable power and homely skill which endeared him to a multitude of readers without his own achieving any recognized place in what is known as "American literature."[17]

Perhaps the integrity and authenticity of some of his fiction will be recognized in time as a valuable picture of a rural and unsophisticated America that is rapidly vanishing. One critic recently remarked to me that C. A. Stephens may survive as a "Currier and Ives of American literature."

Regarding his reputation as a scientific thinker, fate has been paradoxical. Since 1900 there have been great changes in the American climate of opinion — optimism about science has been overshadowed by the anxiety and uncertainty created by two world wars, the depression years and the production of nuclear bombs.[18] As a result the modern reader is likely to consider Stephens's enthusiasm "Victorian" and eccentric. However, there have also been developments that seem to confirm some of his prophecies. The average life expectancy in the United States has been doubled. The virtual "immortality" of tissue cultures has given new grounds for speculation about prolongevity.[19] Interest in geriatrics and in the problems of aging has grown tremendously. If gerontology continues its rapid development, an increased interest in C. A. Stephens may be expected.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42141

PRESENTATION OF CASE

First admission. A nine-month-old male infant was admitted to the hospital because of hematemesis.

The patient was the product of a normal pregnancy and an uneventful delivery. Development was apparently normal until the age of seven months, when blood was discovered on his pillow. A week later the parents noticed a right inguinal hernia and consulted their physician. His findings included tachycardia at a rate of 250, enlargement of the liver and marked edema of the legs. There were no rales or evidence of fluid in the chest. The infant was hospitalized elsewhere. After digitalization, the heart rate fell to 120, the liver decreased in size, and the edema almost disappeared. He was discharged on maintenance digitalis. After discharge, he vomited daily and refused solid foods. His mother noted periods of cyanosis of the lower extremities and lips, especially after sleeping. The cyanosis was not related to crying. On the day of admission, he vomited blood and was referred to this hospital by his physician.

Two siblings were living and well at three and five years of age.

Physical examination revealed a lethargic, chronically ill infant. The right heart border was percussed slightly to the right of the sternum; the left border was 6 cm. to the left of the midsternal line. The heart beat was forceful. A Grade 1, soft, short systolic murmur was heard at the apex and along the left sternal border. The pulmonic second sound was greater than the aortic. An intermittent third sound was heard along the left sternal border. The lungs were clear. Abdominal examination revealed a fluid wave and shifting dullness. A firm liver edge was palpated 4 cm. below the right costal margin. There was a hydrocele on the right and + edema of the legs. There was slight cyanosis but no clubbing.

The temperature was 97.4°F., the pulse 160, and the respirations 28.

Urinalysis was normal. Examination of the blood revealed a hemoglobin of 11.5 gm. per 100 ml. and a white-cell count of 14,000, with a normal differential. The sodium, potassium, carbon dioxide, chloride, phosphorus, protein and fasting blood sugar were normal. The cholesterol was 125 mg. per 100 ml. An electrocardiogram showed first-degree atrioventricular block, minimal right-axis deviation, large, peaked P waves in Lead 2 and diphasic P waves in Lead V_1. X-ray films of the chest showed generalized cardiomegaly and pulmonary congestion.

The administration of Mercuhydrin was followed by diuresis of 1 kg. of fluid. Subsequent electrocardiograms revealed alternating first-degree and second-degree atrioventricular block, the latter varying from 2:1 to 3:2. On the sixth hospital day, the pulse suddenly dropped to 60, and an electrocardiogram showed irregular idioventricular rhythm. The serum potassium was now 6.1 milliequiv. per liter. Later in the day, atrial contraction resumed, but with varying degrees of block. On the eighth hospital day fluoroscopy revealed little if any change in the size or shape of the heart. Pulsations, especially along the left border in the region of the left ventricle, were greatly diminished in amplitude. The pulmonary vessels did not appear significantly engorged. The patient was redigitalized with Digoxin on the eleventh hospital day and was maintained on this drug. Varying degrees of heart block persisted until the sixteenth hospital day, when the rhythm became regular for the first time. Cortisone, 50 mg. daily, was begun. He was also placed on a low-salt diet with added potassium chloride. He was discharged on the twenty-ninth hospital day on a regimen of Digoxin, cortisone, a low-salt diet and potassium chloride. At the time of discharge, his weight was stable, the cardiac rhythm was regular, and there was no peripheral edema. The liver edge, however, was still 3 cm. below the right costal margin.

Final admission (two months later). The patient was well until three weeks before re-entry, when he had a nosebleed, which stopped spontaneously. Two weeks later he vomited over a four-day period. During this time and thereafter the output of urine diminished. Four days before entry, the urine was bright red on four or five occasions. During the week before entry the parents noticed increasing size of the abdomen. On the day before admission they again noted cyanosis of the lips and extremities. Cortisone had been gradually withdrawn three weeks before admission and was no longer being administered at the time of admission. Potassium chloride had been discontinued five days before admission.

Physical examination revealed cardiac enlargement. The lungs were clear. The liver edge was palpable 4 fingerbreadths below the costal margin. There was marked ascites and peripheral edema. The nail beds were cyanotic.

The temperature was 99.7°F., the pulse 140, and the respirations 30.

Examination of the blood revealed a hemoglobin of 10.3 gm. per 100 ml. and a white-cell count of 6100. The sodium was 118 milliequiv., and the potassium 6.2 milliequiv. per liter, and the nonprotein nitrogen 26 mg. per 100 ml. The prothrombin content was less than 10 per cent. An electrocardiogram showed a sinus tachycardia at a rate of 150 and first-degree atrioventricular block (Fig. 1). The PR interval was 0.18 second, and the QRS interval 0.10 second. There were mammoth, bizarre P waves. There was a bizarre P wave in Lead V_1; the R waves equaled the S waves in Lead V_1; there was a QS pattern in Lead V_6. An x-ray film of the chest showed no significant change in the heart, but there was a suggestion of pulmonary congestion (Fig. 2).

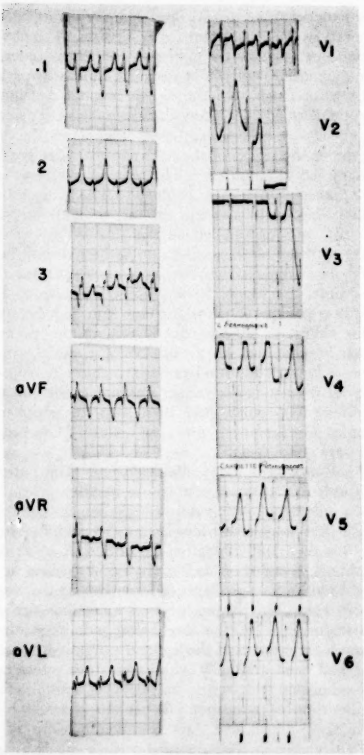

FIGURE 1.

The patient was treated with Digoxin, Meticorten and vitamin K, and was placed on a normal diet without added potassium. An injection of Mercuhydrin was given. By the third hospital day the prothrombin time was 42 per cent of normal, and he had lost 1 kg. of weight. The sodium was now 124 milliequiv., and the potassium 4.7 milliequiv. per liter. On the fifth hospital day a 400-mg. sodium diet was begun. Despite vitamin K given orally, the prothrombin content fell again to around 15 to 30 per cent. On the tenth hospital day the temperature was 101°F., the pulse 160, and the respirations 40 and irregular. Physical examination was as on admission. The white-cell count was 21,600, with 70 per cent neutrophils. The nonprotein nitrogen was 62 mg. per 100 ml. Cephalin flocculation was ++++ in twenty-four and forty-eight hours. The heart rate increased to 190. X-ray films of the chest showed the lungs to be clear. The patient was placed in an oxygen tent and given a supplemental dose of Digoxin (half the daily maintenance of 0.3 mg.). After a paracentesis productive of 700 ml. of straw-colored fluid, respirations improved.

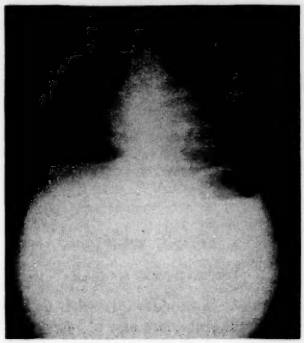

FIGURE 2. *Anteroposterior Film of the Chest, Showing Generalized Cardiac Enlargement and Clear Lung Fields.*

He remained in fair condition, but continued to have generalized anasarca. Electrocardiograms continued to show supraventricular tachycardia with high, peaked P waves. Another paracentesis was performed on the twenty-sixth hospital day, with removal of 400 ml. of fluid. At this time the total protein was 4.4 gm. per 100 ml. The patient's caloric intake was increased. On the morning of the thirty-third hospital day he suddenly died.

DIFFERENTIAL DIAGNOSIS

DR. ALEXANDER S. NADAS*: This is a long, complicated story. I do not know how well this baby was during the first few weeks or months of life, but at seven months he was emaciated and lethargic and looked chronically ill. I shall assume, therefore, that he had not been very well from birth. I do not think

*Cardiologist, Children's Medical Center.

the mother was medically sophisticated, for she did not bring the infant to a physican on account of the hematemesis, but rather because of an inguinal hernia. With all due respect to the dangers of inguinal hernia, I think that hematemesis is a much more upsetting finding. At about the age of seven months hematemesis occurred, and a week later a physician discovered that the child was in congestive heart failure. The congestive heart failure was right-sided; I do not think one can deny that. The diagnosis is based on the presence of an enlarged liver, ascites and edema associated with a large heart. May I see the x-ray films?

DR. C. C. WANG: Examination of the chest on the first admission shows a large heart (Fig. 2); the enlargement appears to involve all the chambers. The pulmonary vessels are, I think, within normal limits. There is no fluid within the pleural cavities. The films of the abdomen demonstrate fluid; the spleen is not particularly enlarged.

DR. NADAS: In the protocol there was the statement that the pulsations of the left border of the heart were diminished. Moreover, the protocol suggests that the patient had some pulmonary vascular engorgement.

DR. WANG: I think that the pulmonary vessels are not engorged.

DR. NADAS: I should say, then, that the patient had right-sided congestive heart failure, enlargement of the heart and enlargement of the liver, with ascites and edema. Whether in addition, before the right-sided failure, he had left-sided failure one cannot say with certainty. However, Dr. Paul D. White has often said that the most common cause of right-sided failure is left-sided failure.

The patient had no significant murmur. When at the Massachusetts General Hospital physicians describe a systolic murmur as Grade 1, one is not suspicious that the murmur is significant. Physicians describe a murmur as Grade 2 or 3 if they think it is meaningful. There were grossly abnormal electrocardiograms. Have you seen those, Dr. Bland?

DR. EDWARD F. BLAND: The P waves are tremendous (Fig. 1).

DR. NADAS: That may mean atrial hypertrophy; I am willing to cross that Rubicon and say that it does mean atrial hypertrophy. The electrocardiogram also suggests disturbance in the conduction system. There was atrioventricular block. I think there was a disturbance also of the intraventricular conduction system; a QRS interval of 0.10 second is a great deal wider than one would expect in a year-old baby. The tracings show a great deal of slurring and notching of the QRS complex. The electrocardiogram does not indicate which ventricle is more hypertrophied; it does give the negative information that the right ventricle was not greatly hypertrophied and indirectly suggests that left ventricular hypertrophy may have been present. There was some further evidence in the electrocardiogram to support this hypothesis in that the S waves in the right-sided chest leads were very deep. If the left ventricular voltage could have been picked up somewhere along the chest it might have corresponded to tall R waves, but none of the conventional or even extra leads demonstrate this.

The congestive heart failure responded well, although temporarily, to anticongestive measures such as digitalis and mercurial diuretics. This puts it into the select group of conditions that in this age will respond well to routine anticongestive measures.

What could the underlying heart condition have been? The first one that one thinks about in children is rheumatic heart disease. I think that I can rule it out on the basis of age, the absence of murmurs and so on.

The second is congenital heart disease such as a communication between the pulmonary and systemic circuits. I would rule most of those out, but I do not have time to analyze the reasons. I do not think that this patient had a major right-to-left shunt through a communication because he was not blue enough long enough to cause death. I do not think he had a major left-to-right shunt through a communication because the pulmonary vessels were not engorged and because murmurs of any significance were not present. Was there something wrong with the valves or the blood vessels within or without the heart? A coarctation of the aorta certainly ought to be considered. I wish somebody could tell me what the blood-pressure recordings on this baby were; none were included in the protocol.

DR. ROBERT E. SCULLY: The blood pressure was 95 systolic, 65 diastolic, on one occasion.

DR. NADAS: How about the femoral pulses?

DR. SCULLY: I do not believe they are mentioned in the record.

DR. NADAS: If femoral pulses were not taken, I cannot discard coarctation of the aorta. It can produce exactly this sort of picture. Aortic stenosis I shall discard because of the absence of a significant murmur. Mitral stenosis, pulmonary vascular disease and pulmonary stenosis can be ruled out because of the absence of evidence of right ventricular hypertrophy in the electrocardiogram and the absence of significant murmurs of pulmonary stenosis. Involvement of the tricuspid valve, such as in Ebstein's disease, I think, has to stay in the race. Tricuspid stenosis also has to be considered.

There is a third group of conditions, the so-called primary myocardial diseases, among which one should consider principally endocardial fibroelastosis and idiopathic myocarditis. The other three members of the family — von Gierke's disease, anomalous coronary arteries and medial necrosis of the coronary arteries — I shall discard because chronic recurrent congestive heart failure is not characteristic of them.

Constrictive pericarditis I mention but do not consider because it does not occur at this age.

In addition to the congestive heart failure, the patient had hemorrhagic manifestations: nosebleeds, hematemesis and bloody urine. The low prothrombin content is a fairly good explanation for all these. Was a platelet count done?

DR. SCULLY: Not that I can find recorded.

DR. NADAS: Why did this patient have a low prothrombin content? Obviously, because he had liver disease. He had a ++++ cephalin flocculation and an amount of ascites greater than is seen in pure congestive heart failure at this age. One then has to attempt to correlate liver disease — causing a low prothrombin content and hemorrhagic manifestations — with heart disease. Can this be done? The baby was too young to have severe cardiac cirrhosis as a result of congestive heart failure; I think that usually more time is needed for varices and cardiac cirrhosis of this magnitude to develop on the basis of congestive heart failure alone. Should I say, then, that the two diseases were entirely unrelated? When discussing a case representing two apparently different conditions in this amphitheater, we would be foolish not to look for a common etiology. Since I cannot believe that the liver disease caused the heart disease or vice versa I am left with the proposition that the liver disease and the heart disease were an expression of a common etiologic factor. An intra-uterine infection, such as one due to the Cocksackie virus or cytomegalic inclusion bodies, could have caused heart disease and hepatitis with cirrhosis and started the whole chain of events. One is then left with myocardial fibrosis of infectious etiology; the same intra-uterine infection may have caused liver disease, cirrhosis and the death of the patient.

DR. SCULLY: Dr. Bland, will you comment on this case?

DR. BLAND: At the first admission we discussed the problem at cardiac rounds; we did not know what was wrong with the child. Dr. Gordon S. Myers and I leaned toward Ebstein's malformation, but we did not feel very strongly about it. Therefore, we recommended the cortisone in the hope that we were wrong and that this might be a form of myocarditis that would quiet down. I do not think that the Service came any closer to the diagnosis than that.

I was not sure how you eliminated the possibility of von Gierke's disease, Dr. Nadas.

DR. NADAS: The first reason that I discarded von Gierke's disease was that one year of age is a little old. Secondly, I find it difficult to explain the liver disease on that basis. Thirdly, from what I know of the literature, von Gierke's disease is not as likely as the other members of the primary myocardial disease family to give rise to chronic congestive heart failure.

DR. BLAND: Patients with von Gierke's disease do not live long enough to exhibit chronic congestive heart failure.

DR. NADAS: I suppose that is the reason.

CLINICAL DIAGNOSIS

? Ebstein's malformation of tricuspid valve.
? Idiopathic myocarditis.

DR. ALEXANDER NADAS'S DIAGNOSIS

Intra-uterine infection, resulting in myocardial fibrosis and cirrhosis of liver.

ANATOMICAL DIAGNOSES

Idiopathic cardiac hypertrophy.
Chronic passive congestion of liver, severe.
Interstitial pneumonitis.
Ascites.
Hydrothorax, slight, bilateral.

PATHOLOGICAL DISCUSSION

DR. SCULLY: At autopsy the heart weighed 100 gm., whereas the normal weight for this age is 44 gm. The enlargement was generalized; the left ventricle measured 15 mm., and the right 7 mm. in thickness. The right atrium and especially its appendage were greatly dilated. There was no thickening of the endocardium in any of the chambers so that this was not a case of fibroelastosis. We were unable to find any congenital defects we considered significant. There was, however, a slight abnormality of the tricuspid valve. The right leaflet was quite long and apron-like; many of its chordae tendineae were very short — about 2 mm. in length. The left leaflet showed anomalous insertion of its chordae; although some of them were attached to the tip of the anterior papillary muscle, several were inserted far down near the bases. Minor abnormalities of the atrioventricular valves and their chordae are seen from time to time and as a rule have no significance. I suppose it is possible that this anomaly, which was more marked than one usually encounters, caused some insufficiency and contributed to the right-sided failure, but it seems unlikely. However, not having perfused the heart at postmortem examination,[1] we have no way of being certain. The microscopical sections of the heart were not remarkable except for the presence of minor areas of degeneration of the myocardium — areas of so-called myocytolysis — in which small groups of muscle fibers had dropped out. The coronary arteries appeared normal, and we were unable to find any changes in the systemic arteries such as have been described in the literature in some cases of infantile cardiac hypertrophy.[2] For lack of a better diagnosis, I think we shall have to classify the heart disease in this case as idiopathic cardiac hypertrophy.

The liver was enlarged about 50 per cent over its normal size. On cut section it showed a striking nut-

meg appearance. Microscopically, there was severe chronic passive congestion. In many areas the liver parenchyma was completely replaced by blood. In other regions, which appeared yellowish grossly, there was a fair amount of regenerated liver tissue. In the areas where the liver cells were intact there was bile stasis, indicating an unusually severe degree of congestion. There was no evidence of any other disease in the liver.

The abdominal cavity contained 600 ml. of fluid; there were 50 ml. of fluid in each pleural cavity and 30 ml. in the pericardial cavity. There was no chronic passive congestion in the lungs. However, there was a moderately severe interstitial pneumonitis, which had probably occurred within the last few days of life. There was likewise a moderate amount of pulmonary congestion and edema; I think that one can explain this by the pneumonitis without evoking left-sided cardiac failure as a cause.

Idiopathic cardiac hypertrophy was a common diagnosis in infants fifteen or twenty years ago, but since that time most of the cases have been reclassified as endocardial fibroelastosis because of the finding of marked endocardial thickening, especially in the left ventricle. When Thomas and his co-workers[3] went over our cases of idiopathic cardiac hypertrophy in infancy over the past twenty-five years they reclassified all of them as endocardial fibroelastosis. This then is the first case of idiopathic cardiac hypertrophy in infancy that we have in our recent files.

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CASE 42142

Presentation of Case

A seventy-one-year-old widow was admitted to the hospital because of abdominal pain.

During the previous six months she had occasionally noted abdominal pain in the right upper quadrant that was unrelated to meals. One month before admission the pain recurred and persisted for four days. She was admitted to another hospital for two weeks. X-ray films demonstrated a normal gall bladder. An abdominal film was normal except for osteoporosis of the lumbar vertebras. A barium-enema examination showed diverticula in the descending colon. The white-cell count ranged from 13,200 to 17,000. The pain, which had subsided to a dull ache, recurred one day before admission and persisted; it was sharp, knifelike and nonradiating. For several days before entry the urine had been dark. Since the onset of the illness there had been slight anorexia. There was no jaundice, fatty-food intolerance, nausea, vomiting or melena, nor were there chills, fever or clay-colored stools. There was no history of alcoholism.

Physical examination revealed an obese, noisy, uncooperative woman complaining of abdominal pain in the right upper quadrant. There was no jaundice. Examination of the chest was negative. The liver edge, which was felt 9 cm. below the right costal margin, appeared to be involved by a firm, tender mass. The spleen was not palpable. There was ++ pretibial edema. Neurologic examination was negative.

The temperature was 98°F., the pulse 96, and respirations 22. The blood pressure was 140 systolic, 70 diastolic.

The urine gave a + test for albumin and a negative test for bile; the sediment contained 15 white cells and a rare red cell per high-power field; culture grew out a few coliform bacilli. The urinary urobilinogen was 0.7 Ehrlich units. Examination of the blood revealed a hemoglobin of 14.4 gm. per 100 ml. and a white-cell count of 15,700, with 77 per cent neutrophils. The serum nonprotein nitrogen was 10 mg., the total protein 6.1 gm., the albumin 3.4 gm., the globulin 2.7 gm., the cholesterol 263 mg., the cholesterol esters 103 mg., the bilirubin 1.3 mg., and the fasting blood glucose 118 mg. per 100 ml. The amylase was 14 Russell units, the transaminase 81 units, the alkaline phosphatase 18.7 units, and the cholinesterase 0.41 delta pH units per hour. Cephalin flocculation was negative in forty-eight hours. The thymol turbidity was 1.5 units, with a negative flocculation test. The prothrombin content was 50 per cent. The bromsulfalein retention was 66 per cent. An x-ray film of the chest showed calcification in the aortic knob; the heart and lungs appeared normal. An abdominal film demonstrated a prominent liver with the edge lying close to the right iliac crest; calcification was noted in the middle portion of the abdomen on the right side. An upper gastrointestinal series was normal. A barium-enema examination demonstrated diverticula throughout the descending and transverse colon. Except for frontal endostoses in the skull and degenerative changes throughout the dorsolumbar spine, films of the skull, dorsolumbar spine and pelvis were normal. An electrocardiogram showed a normal sinus rhythm at a rate of 100; the PR and QRS intervals were 0.14 and 0.08 second respectively; there was slight slurring and depression of the ST segments, with low to diphasic T waves in Leads 1, aVL, V_5 and V_6; the T waves were inverted in Leads 2, 3, aVF and V_1 through V_4.

Therapy included sedation and Hykinone, 10 mg. daily. On the eighth hospital day the patient appeared mildly obtunded. She was responsive but inattentive and drowsy. Physical examination revealed a right-sided flaccid hemiparesis. The pupils were markedly constricted; the left pupil did not react. There was questionably impaired conjugate gaze to

the left. The temperature was normal, the pulse 100, and the respirations, which were deep and regular, 32. The blood pressure was 90 systolic, 60 diastolic. Lumbar puncture yielded 5 ml. of clear cerebrospinal fluid containing 2100 red cells per cubic millimeter; the initial pressure was equivalent to 80 mm., and the final pressure to 50 mm. of water; the Pandy test was negative. Examination of the blood showed a white-cell count of 25,000, with 90 per cent neutrophils. The sodium, potassium and chloride were normal. The nonprotein nitrogen was 32 mg. per 100 ml., and the serum water 291 milliosmols per liter. The prothrombin content was 28 per cent. Hykinone therapy was stopped. The patient gradually became less responsive and was unable to communicate or swallow. On the ninth hospital day lumbar puncture revealed normal dynamics and yielded 3 ml. of clear cerebrospinal fluid containing 53 red cells per cubic millimeter with a total protein of 40 mg. and a glucose of 100 mg. per 100 ml.; the gold-sol curve was normal, and culture showed no growth. Bright-red blood was noted in the nasopharynx the next day. Mephyton and Hykinone were given intravenously, and Synkayvite was given intramuscularly. Physical examination showed, in addition to the previous findings, cyanosis and coldness of both feet. The dorsalis pedis and posterior tibial pulses, which had been previously present, were absent bilaterally. The liver felt stony hard and questionably nodular. There was no pain perception. She died on the tenth hospital day. Terminally, considerable bright-red blood was noted in the nose and posterior nasopharynx.

Differential Diagnosis

Dr. Earle M. Chapman:* The liver edge noted at the iliac crest in the x-ray films seems lower than 9 cm. below the right costal margin. I think we should pause for demonstration of the x-ray films.

Dr. Richard V. Wilson: I am not going to be able to help much. The liver edge seems to be at a level about 9 cm. below the right costal margin; however, we cannot exactly determine the size of a liver on a film.

Dr. Chapman: From the report I had visualized it as lower.

Dr. Wilson: It really is not at the iliac crest, but just above it. In addition, the report implied that there were many diverticula in the colon, but actually there are comparatively few and these are quite insignificant. I do not see any masses. The liver edge is perfectly smooth. I see no bone destruction. The films of the chest look normal.

Dr. Chapman: What is this calcification?

Dr. Wilson: That is not calcification; it is gallbladder dye. The day before, according to the x-ray reports, the patient must have had a Graham test although I find no films from a Graham test; the x-ray report says that the gall bladder was not visualized on a cholecystogram.

Dr. Chapman: There is the note of a negative x-ray examination of the gall bladder at another hospital.

Dr. Wilson: Unfortunately, I have no films. I should think that the patient had received pills.

Dr. A. Robert Arnstein: As I recall, she took 2 or 3 pills, but not enough so that the gall-bladder test could be done.

Dr. Chapman: In this hospital?

Dr. Wilson: Yes, I believe so.

Dr. Chapman: Dr. Wilson, can you define the right-kidney shadow?

Dr. Wilson: The upper pole and the lateral margin are outlined; I do not see the lower pole on this film, but on some of the other films it was visible.

Dr. Chapman: Does it look normal?

Dr. Wilson: Yes, but we do not have an intravenous pyelogram.

Dr. Jacob C. Lerman: Is the right leaf of the diaphragm high?

Dr. Wilson: Yes; it is higher than it should be.

Dr. Chapman: The contour of the heart does not suggest chronic pericarditis, does it?

Dr. Wilson: It does not suggest pericardial fluid; I do not see any calcification. Fluoroscopy was not carried out. Only this portion of the shadow is the apex of the heart; the remainder is epicardial fat pad, so that the cardiac shadow is of normal size.

Dr. Chapman: The problem is to define the cause and effects of an enlarged, painful liver without enlargement of the spleen that proved fatal in six months to an elderly woman in whom there was no history of antecedent liver injuries, infections, toxins or poor nutrition.

That failure of liver function was the principal cause of death is attested by the clinical state with pretibial edema and by the laboratory evidence of a high alkaline phosphatase, a low prothrombin content, a marked degree of bromsulfalein retention in the serum and the very low nonprotein nitrogen because the liver was unable to synthesize urea from ammonia. Aminoaciduria was probably present but was not measured. The consequence of a low prothrombin content may be bleeding into tissues. In the patient under discussion this seems to have occurred into the nose, the pericardium and the brain: the nosebleeds were described; the electrocardiogram — the inversion of T waves without changes in the Q waves — is consistent with pericarditis or the extravasation of blood into the pericardium (in fact the terminal failure in circulation indicates cardiac tamponade); and the right-sided hemiparesis with a fixed left pupil favors left-sided cerebral anoxia, probably from hemorrhage, and not the torpid mental state that is often seen in cholemia without demonstrable pathological changes.

Therapy in this case seems to have consisted of re-

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peated lumbar punctures and repeated injections of a variety of vitamin K preparations. The lumbar punctures revealed little except the few red cells found in the cerebrospinal fluid. The prothrombin content continued to fall in spite of the vitamin K. Deficiency of vitamin K occurs under two conditions: when bile cannot reach the intestines and hence vitamin K is not absorbed; and when there is severe liver-cell injury even though bile reaches the intestinal tract. In the first condition, injections of vitamin K restore the prothrombin level in a few hours; in the second, they are usually without effect on the prothrombin level because the liver-cell failure is advanced — but it makes the clinician feel better.

Now that I have blamed the liver as the source of this woman's trouble, what was the cause of its enlargement? It was not engorged with bile because there was no jaundice, and the blood bilirubin was only slightly elevated. The biliary tract was intact. Was it engorged with blood? I doubt it. The heart sounds were not described, and although the changes in the electrocardiogram are those seen in pericarditis, there was no supporting evidence for this diagnosis or for myocardial infarction. In the nutmeg liver of chronic congestion, the bromsulfalein retention and alkaline phosphatase may be elevated, but not to the degree recorded; besides, the short duration of the illness is against the central scarring said to be typical of cardiac cirrhosis. Was the liver infiltrated with fat, glycogen, lipoid or amyloid? No.

Was the liver the site of inflammation or some form of hepatitis? The answer here is not easy. The white-cell count was much higher than that usually seen in liver failure. If the first appearance of right-upper-quadrant pain represented the primary injury to the liver from massive necrosis, the subsequent course may have indicated chronic inflammation irregularly distributed in the liver and distorting it with the areas of regenerative hyperplasia. In such cases the liver edge may be coarsely nodular; frequently, the left lobe is involved more markedly than the right. If the lesion progresses slowly, portal obstruction with enlargement of the spleen may appear relatively late. This is the syndrome of postnecrotic scarring and may be the result of one of several injuries to the liver.

One other possibility is that the vascular supply to the liver was in some way occluded, that the sharp pain represented injury from anoxia and that the subsequent course represented the reactions to massive necrosis with rapid regenerative hyperplasia. Massive infarction of the liver is rare and is usually accompanied by more signs of shock than this patient had, and the outcome is rapidly fatal.

In such scarred livers with regenerative nodules the process of cellular growth becomes uncontrolled and leads to neoplasia. Primary cancer nearly always develops in the liver that has been previously injured and hence shows both fibrosis and nodules of hyperplasia. Although the cancer usually originates in a single area, it may be multiple. A liver biopsy would have settled the point.

My assumption is that the liver cancer grew rapidly, that the pain and tenderness grew worse and that the destruction of functioning liver cells progressed so rapidly that the patient did not lose much weight or have the expected anemia. A high white-cell count is seen from central necrosis or rapidly growing tumor that acts like an abscess. I have seen 1 case in which the primary tumor was in the right kidney and by extension involved the liver. If this was so in the patient under discussion the pericardial and cerebral symptoms can be explained better by metastases. Since Dr. Wilson assures me that the right kidney was normal, I think that this is a remote possibility. If this tumor in the liver was a metastasis there was no evidence radiologically of the primary site. I have chosen to believe that the hemiparesis was the result of hemorrhage and not of a metastasis.

DR. JOHN T. QUINBY: You mentioned the value of a liver biopsy; do you think it would have been safe to do one on this woman?

DR. ARNSTEIN: A liver biopsy was planned after a course of parenteral vitamin K therapy that we hoped would raise the prothrombin content.

DR. REED HARWOOD: Do you think that there was bleeding into the pericardium?

DR. CHAPMAN: I cannot be certain; the absence of Q-wave changes does not fit with myocardial infarction. If this represented infarction, it was a bizarre pattern of extensive myocardial infarction involving apparently the anterior and posterior walls and perhaps even the septal wall, but there should have been some Q-wave changes.

DR. HARWOOD: The patient was elderly and may well have had small myocardial infarctions.

DR. CHAPMAN: She may have had a scar.

DR. HARWOOD: If she bled into the pericardial sac she should have died immediately or have had severe chest pain.

DR. CHAPMAN: She did not have chest pain. She could have had an old scarred myocardium from previous insults, which were not mentioned in the history. Such scars could have inverted the T waves, but I wonder why the Q waves were not described.

DR. EDGAR B. TAFT: All that is mentioned in the description of the electrocardiogram is that the QRS complex was normal.

DR. CHAPMAN: The cardiac silhouette was normal.

DR. WILSON: Yes; the film of the chest was taken shortly after admission, though.

CLINICAL DIAGNOSES

? Thrombosis of left middle cerebral artery, with right hemiplegia.
Metastatic carcinoma of liver from pancreas.
Popliteal-artery thrombosis.
? Myocardial infarction.

Dr. Earle M. Chapman's Diagnoses

Hepatoma.
Cerebral hemorrhage.

Anatomical Diagnoses

Cholangioma of liver, with metastases to lymph nodes of porta hepatis.
Hemorrhagic infarction of left temporal and occipital lobes due to probable embolic occlusion of left posterior cerebral artery.
Multiple tiny embolic infarcts of brain.
Infarcts of spleen and kidneys, ? embolic.
Pulmonary embolism, with infarction, multiple, recent.
Thrombosis, old and recent, of iliac veins.

Pathological Discussion

Dr. Taft: At autopsy the heart showed only mild coronary sclerosis. The problems that this woman presented can be divided into two groups anatomically: one was of embolic and thrombotic nature, which is somewhat disconcerting to me in the light of the low prothrombin content; the other was a malignant process. There were thrombi in the leg veins bilaterally; most of these thrombi were old and organized, but in each of the iliac veins there were fresh, dark-red, only slightly adherent ante-mortem thrombi. The lungs were somewhat heavy and contained numerous small infarcts; there was one large infarct in the right lower lobe, approximately 8 cm. in greatest diameter. These were hemorrhagic and microscopically were recent and probably had occurred within forty-eight hours of death. In addition there were recent infarctions in both kidneys, the spleen and the brain. The left posterior cerebral artery was occluded at two points by firm, pale-gray material, which distended the vessel and which microscopically was composed of fibrin with a few enmeshed neutrophils. There was no reaction of the vessel wall. This appearance is consistent with embolic material. There was a recent hemorrhagic infarct of the left posterior temporal and occipital lobes, which is also consistent, as probably you all are aware, with embolic infarcts. In addition, on section of the brain, numerous tiny areas of infarction were seen scattered through the white matter and cortex. Some of these microscopically were associated with small vessels occluded with similar material to that found in the left posterior cerebral artery.

All the areas of infarction in the kidneys, spleen and brain suggest that there were emboli arising from some thrombotic process in the left side of the heart. There was no gross evidence of disease in the chambers of the heart. The microscopical appearance of the material found in the cerebral arteries is consistent with so-called nonbacterial marantic endocarditis, which is fairly commonly seen in elderly patients and often in patients with cancer. However, I cannot say from the anatomical point of view that such disease was present; there was no evidence of such a process at the time of autopsy. If it had been present, all the material must have broken off as emboli before death.

The liver was the most remarkable organ; it weighed approximately 3000 gm. The surface of the left lobe looked relatively normal. When it was cut the major portion of the liver was seen to be occupied by a large tumor mass, some of which was cystic and some of which appeared to be yellow and necrotic. There were a few smaller areas of tumor scattered throughout the liver. The gall bladder was normal. The bile ducts outside and within the liver and the hepatic and portal veins were normal. There were two slightly enlarged lymph nodes in the porta hepatis, but these did not press on the bile ducts. There was no tumor elsewhere in the body. The pancreas was normal, as were the various endocrine organs. The lack of evidence of other tumor suggests that this was a primary tumor. We thought at first, from its gross appearance, that it was a primary bile-duct tumor — a cholangioma rather than a hepatoma because there was no apparent cirrhosis. Almost all the primary liver-cell tumors occur, as Dr. Chapman suggested, on the basis of pre-existing cirrhosis. Microscopically, this tumor was quite undifferentiated. In some areas it suggested a papillary pattern and in others an adenocarcinomatous pattern. This arrangement of the tumor cells that in some areas was characteristic of an adenocarcinoma suggests that the tumor was of ductal origin.

Dr. Chapman: Is it not surprising that a tumor that was primary in the bile-duct system grew to this size without causing more clinical jaundice?

Dr. Taft: Apparently, the tumor did not press upon any of the larger bile ducts or interfere with excretion from other parts of the liver. Similar tumors in rats often have an extraordinarily high alkaline phosphatase content.* I wondered, as I read the protocol, whether the high alkaline phosphatase in the serum was a manifestation of its formation in the tumor rather than of bile-duct obstruction. I know of no clinical or pathological evidence to support this, however.

*Pearson, B., Novikoff, A. B., and Morrione, T. G. Histochemical localization of alkaline phosphatase during carcinogenesis in rats fed *p*-dimethylaminoazobenzene. *Cancer Res.* **10**:557-564, 1950.

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MORE LOST HORIZONS

THERE is difficulty in maintaining a sense of proportion in a period when so much that is being offered appeals to the desire for material things; when temporal gratification seems often to outweigh all other considerations. It is particularly the case when so many have the means for acquiring so much with apparently so little conception of the true values in life; when the man with the dollar has become the target of every sharpshooter on the firing line of mass production.

The general rule applies to the objectives of many of the world's gigantic industrial efforts, from the marketing of automobiles (in which the year's new model, by some fictitious necromancy, is credited to popular demand), to the products of zymurgy, dealing with the processes of fermentation, as in brewing. There seems, unfortunately, to be no purchasable contentment, prosperity resulting rather in appetite stimulation than in its appeasement.

Pharmaceutical manufacturing is the industrial enterprise most directly related to the practice of medicine, occupying a special position between the purely practical and sometimes sordid business of selling goods to an artfully created market, with no holds barred, and an accepted moral obligation to serve mankind and do it no harm. On its highest level it is in partnership with science and the healing art; on its lowest it is a strictly commercial adventure, exploiting the tremendous advances in chemistry and biology that have both increased its ethical responsibilities and its opportunities for ignoring them. "No man," according to a still recognized authority, "can serve two masters: for either he will hate the one and love the other; or else he will hold to the one and despise the other. Ye cannot serve God and mammon."

Examples of this loss of values are not hard to find. A recent illustration is the sudden tumble of *Time* from an acceptably restrained level of reportorial responsibility to a sensational relating of the widespread over-the-counter demand for a mood-controlling drug with all the potential risks inseparable from any agent with such dynamic possibilities. Here, under the heading "Don't-Give-a-Damn Pills," meprobamate is breezily heralded as the fastest selling pacifier for the frustrated and frenetic, the backlog of unfilled orders being at once the pride and despair of the commercial laboratories that produce it.

Obviously an agent with rather frightening possibilities unless used under competent guidance, meprobamate has been dispensed by one Los Angeles drug store to a grand total (at that time) of 250,000 pills, with more orders turned away than can be filled. The craving (sic!), moreover, is not restricted to Hollywood. "In staid Boston the demand is as keen, but less shrill. It is the same in New York City, Washington, D.C., Charlotte, N.C., and Houston, where drug-

gists refuse to fill prescriptions for strangers, often have to limit regular customers to a dozen pills on account while they wait for an overdue shipment." Were such a sales volume on prescription alone, which may reasonably be questioned, then some members of the medical profession itself would have something on their consciences.

Morning, noon and night the more sophisticated elements of the human race, regardless of basic education, are coming to rely more and more on chemical agents to stimulate and sedate, to change their moods and regulate their bowels. With one hand they fight off old addictions, to caffeine and cathartics, to tobacco smoke and alcohol and hypnotics, while with the other they smooth the way to new addictions in the constant effort to escape beyond the prosaic limits of personality and subdue the pains of existence. What a pity that *Time* must make a Roman holiday of the predicament!

The lay press, however, may still be excused because of ignorance and its own addiction to sensationalism. What cannot be excused is the type of unsavory episode that recently took place in which a prominent pharmaceutical manufacturer, also with a mood ameliorator to sell — like the others, a new and exciting one — issued a "Dear Doctor" letter to physicians advising them that the wonder drug would soon be available and deprecating the prerelease publicity for which those "busy reporters" were responsible.

Unfortunately a telegram, dated eight days before the letter, had apparently been transmitted to an unknown number of lay periodicals inviting them to send representatives as guests of the manufacturer to a hospital staff meeting to be held thirteen days later, when the wraps would be taken off the new ataractic (which had been developed, according to other sources of information, by a firm of French chemists) with more than the usual sound effects. "YOU WILL SEE ACTUAL CASES OF DELIRIUM TREMENS DRUG ADDICTS AND PSYCHOTICS IN THE PROCESS OF THERAPY ON A TOUR OF WARDS FOLLOWING THE STAFF CONFERENCE. YOU WILL ALSO SEE AN UNCENSORED SOUND AND COLOR MOTION PICTURE OF THE HOSPITAL'S EXPERIENCE THUS FAR WITH THE DRUG FOR THE PICTURES. THE LADIES ARE WARNED TO PROVIDE THEIR OWN EAR PLUGS."

If, as *Time* intimates, the new series of so-called tranquillizing agents produces a don't-give-a-damn attitude, then it provides what a few, at least, of the manufacturers already have.

DECLINE OF CERTIFIED MILK

It is one of the frustrating aspects of human endeavor—perhaps a minor one—that as the quality of certified milk gets better and better the demand for it grows less and less. And yet perhaps it is not so paradoxical as it seems, for most of the fresh milk marketed in this area has become so clean as to be practically spotless.

Certified milk, nevertheless, the aristocrat of lacteal fluids, has retained a certain aura of qualitative supremacy over ordinary varieties from and for the common herd, superior as these products have become. Not only is its nutritive content standardized but it has become almost fantastically pure. Thus, during the past year no single bacteria count on milk certified by the Boston Medical Milk Commission has exceeded 2000 colonies even before pasteurization, and only 10 of some 150 counts have exceeded 1000, which represents very clean milk indeed; the souring of such milk is a tedious process. The counts on the same milk when pasteurized exceeded 20 on only one sample and were usually under 5. Since all the milk is pasteurized it may be considered as reasonably close to sterile.

Rarely were coliform organisms found even in the raw milk; the fact that they occur at all helps to explain the local requirement of pasteurization for all milk, certified or not. The difficulty of eradicating these organisms indicates the problem that exists down on the farm in respect to the removal of manure, especially in winter, and suggests the effectiveness of flush toilets were it not for the limited capacity of cattle to respond to more than the most rudimentary training. Moreover, those scientific agrarians who have been schooled in the principle of the nitrogen cycle may still cleave to the advantages of a little natural dressing when fields lie ready for tillage.

The sixty years that have elapsed since the introduction of certification have seen great changes in the production, packaging and distribution of milk in general. In the beginning certification was a sincere and successful effort to produce a raw milk that could be fed to infants with a reasonable chance of their survival; certified milk, produced, bottled and distributed under rigid controls, led to the introduction of regulations that have made relatively clean practically all milk that comes to urban markets. In so doing it has, of course, reduced its own relative value without the benefit of a corresponding reduction in its relative cost, and its steady decline in sales indicates an uncertain future.

The Boston Commission now certifies only two farms, since the Walker-Gordon Farm at Charles River Village, bearing a name associated from the beginning with certified milk, went out of the business of its production. The remaining two farms produced 81,367 quarts of certified whole milk in October, 1950, and 47,884 quarts in October, 1955. In the same five years the total amount of certified whole milk produced in the New England area has dropped from approximately 185,000 quarts per

month to 48,000—a loss of 74 per cent. Only a rise in the sale of certified skim milk,—and skim milk is scarcely a product that one would think of as requiring certification,—has prevented an economic debacle.

Certified milk suffers from a loss of that indispensability that it once possessed for those who knew that it was practically the only reliably clean and safe fresh raw milk; it suffers from an increasing prevalence of cash-and-carry marketing and, partly on account of the lack of such an economical sales outlet, it suffers from its current 7-cent price differential per quart.

The experience is country-wide, with the possible exception of those areas where certified milk is synonymous with raw milk and the price differential is only about 2 cents a quart. In other localities farms have abandoned certification, and milk commissions have ceased to operate. The question is pending whether certified milk should be considered as having fulfilled its destiny and completed its mission, or whether it may still have some old or new function to perform.

MANHATTAN SOCIETY CELEBRATES SESQUICENTENNIAL

A HUNDRED and fifty years ago today—no short period in the history of a nation whose original settlement is little over three hundred years old—102 physicians assembled on the steps of New York's city hall and proclaimed the existence of the Medical Society of the County of New York. As if by prearrangement the Society's charter was then received from the State, and the deed was done. In the midst of the turmoil of New York as now known the historic event has been re-enacted on this sesquicentennial occasion.

As a matter of historical record this very adequate tail wagged so effectively that in the following year the entire dog materialized, like the Cheshire cat in reverse, in the form of the New York State Medical Association.

The County of New York, viewed from the geopolitical angle, consists exclusively of that rock-bottomed strip of territory known as the Island of Manhattan, and one may well believe that the County Medical Society, if not the first fruit of Manhattan's settlement, is at least today its most conspicuous one; the single cherry in the bottom of the glass. For what the Society does in various matters, according to a contemporary release on the subject, "reflects upon the entire profession of medicine across the nation. Its every act is taken in the bright searchlights of the nation's center of press, radio and television and great newspapers and magazines having national distribution."

The Medical Society of the County of New York—the largest local organization of its kind in the country, with its 7000 members—is of practically the same numerical size as the Massachusetts Medical Society. In point of age the two may also be compared, for the Massachusetts Society, celebrating this year the hundred and seventy-fifth anniversary of its incorporation, is the senior by less than a generation.

Antiquity does not necessarily mean substance but it does add flavor. Substance must be in each generation a contemporary contribution. For the substance of its present activities, the culmination of a century and a half of growth and development, the Medical Society of the County of Gotham (Manhattan) is saluted on this historic occasion.

REHABILITATION IN THE PATTERN OF MEDICAL CARE

THE prospective construction, in New England, of the country's first rehabilitation center under the provisions of the Hospital Survey and Construction Act (Hill-Burton Program) is significant not only to the medical profession but to all inhabitants of the area. Two grants have been awarded the Boston Dispensary's Rehabilitation Institute at the New England Medical Center for the construction of its $800,000 Institute Building: $250,000 from Massachusetts in December, 1955; and $50,000 from Maine, as recently announced by Dr. Frederick T. Hill, chairman of Maine's committee on the disbursement of funds provided for hospital construction under the Wolverton Amendment to the Hospital Survey and Construction Act, and Dr. Dean Fisher, commissioner of health.

This special hospital will provide self-help accommodations for 46 inpatients, with separate facilities for both hospitalized and ambulatory adults and children. In addition to medical and surgical supervision, its services will include special occupational and prevocational workshops; an enlarged hydrotherapy and physical-therapy department; a remedial gymnasium; and facilities for speech therapy and psychologic and vocational evaluations and guidance. With these additional facilities, the enlarged Rehabilitation Institute will quadruple its capacity, and will serve the entire New England area.

The new institute, together with such centers as the Shattuck Hospital, operated by the Commonwealth of Massachusetts for the study and rehabilitation of the chronically ill,[1] will take an important place among state and national efforts to broaden the scope of medical care for the handicapped. The entire program is made possible by the Wolverton Amendment to the Hospital Survey and Construction Act,[2] which added nursing homes, outpatient facilities and rehabilitation centers to the list of activities receiving federal support. Rehabilitation as a medical function is thus becoming a vital part of the nation's concern for the welfare of its citizens.

References

1. Rehabilitation at Boston University. *New Eng. J. Med.* **252**:961, 1955.
2. Hospital survey and construction program and its amendments. *New Eng. J. Med.* **254**:290, 1956.

SUFFOLK DISTRICT MEDICAL SOCIETY

The annual meeting of this Society was held in the new hall of the Massachusetts Medical Society, in the Perkins Building, Temple place, on Wednesday, April 2d, at 4 o'clock . . . The large attendance and the interest manifested at this meeting, indicate that the members will be disposed to avail themselves of their excellent quarters, and make the monthly meetings for medical improvement a source of enjoyment and profit to themselves, and of benefit to the profession.

Boston M. & S. J., *April 10, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Post-Partum Hemorrhage

A thirty-four-year-old gravida II, para I, died immediately post partum after an uneventful prenatal course, labor and delivery.

Admitted in active labor with membranes intact, she had an intense three-hour labor, a normal infant, weighing 4.3 kg. (9 pounds, 9 ounces), being delivered half an hour after spontaneous rupture of the membranes under spinal anesthesia. A median episiotomy was performed, the baby being delivered normally as a right occiput posterior presentation. Intramuscular injection of Ergotrate was given, followed in six minutes by delivery of the intact placenta. Within half an hour, excessive flowing was noticed, and an intravenous drip of Pitocin was started, with additional Ergotrate. In spite of this, the fundus remained soft, and flowing continued excessively. One hour post partum the blood pressure was recorded at 80 systolic, 60 diastolic. At that time the uterus was explored and found to be intact and empty, after which it was packed and a small laceration of the cervix was repaired. One hour later 500 ml. of blood was started, but very soon it became apparent that the patient was bleeding through the pack. Pulse and blood pressure now suddenly became unobtainable. At this point, two and a half hours post partum, a further blood transfusion was started under pressure, and a rapid supracervical hysterectomy was done under light cyclopropane anesthesia. At operation a 4-cm. submucous fibroid was found in the flaccid but otherwise normal uterus without intraperitoneal hemorrhage. Despite this surgery and the usual emergency measures, including plasma expander, epinephrine, DOCA and 7 further units of blood, the patient's condition continued to deteriorate and she died in profound shock eight hours post partum, or five hours after hysterectomy.

This case was classified as a preventable death due to hemorrhage. The primary avoidable factor could be stated as transfusion given too late in amounts that were too small. As always, one wonders whether the volume of bleeding immediately post partum, particularly after the physician left, was not grossly underestimated. The unusually large size of the baby, of course, suggests the possibility of post-partum uterine atony; it is regrettable that intravenous injection of Ergotrate was not given immediately after the third stage. One wonders further whether the uterus was held bimanually from above by an attendant for forty-five minutes, a technic that must be considered mandatory in any good institution and might have been life saving in this case.

John Figgis Jewett, M.D.
Chairman

DEATHS

Forsley — Edward T. Forsley, M.D., of Pittsfield, died on February 3. He was in his forty-eighth year.

Dr. Forsley received his degree from Tufts College Medical School in 1933. He was a former president of the Berkshire District Medical Society, chief-of-surgeons and former president of the staff at St. Luke's Hospital, a fellow of the American Medical Association and a member of the International College of Surgeons.

He is survived by his widow, three sons and a daughter.

Hewett — Arthur J. Hewett, M.D., of Newburyport, died on February 25. He was in his seventieth year.

Dr. Hewitt received his degree from the Chicago College of Medicine and Surgery in 1912. He was a fellow of the American Medical Association.

He is survived by his widow, two sons and two daughters.

Hopkins — Ralph Harrison Hopkins, M.D., of Boston, died on March 1. He was in his sixty-fifth year.

Dr. Hopkins received his degree from Boston University School of Medicine in 1915. He was professor of ophthalmology, emeritus, at Boston University School of Medicine, formerly chief eye surgeon of Massachusetts Memorial Hospitals, a fellow of the American College of Surgeons and a member of the New England Ophthalmological Society.

He is survived by his widow and a son.

Leslie — Charles Thomas Leslie, M.D., of Pittsfield, died recently. He was in his seventy-sixth year.

Dr. Leslie received his degree from Columbia University College of Physicians and Surgeons in 1905. He was a past-president and treasurer of the Berkshire District Medical Society, chief-of-staff at St. Luke's Hospital in 1941, and a past member of the Massachusetts State Medical Council.

He is survived by his widow.

MONKS — John Peabody Monks, M.D., of Lincoln, died on March 3. He was in his fifty-fifth year.

Dr. Monks received his degree from Harvard Medical School in 1928. He was a fellow of the American Medical Association and a member of the Association for the Advancement of Science.

He is survived by his widow and three daughters.

PRATT — Joseph H. Pratt, M.D., of Andover, died on March 3. He was in his eighty-fourth year.

Dr. Pratt received his degree from Johns Hopkins University School of Medicine in 1898. He was professor of clinical medicine, emeritus, at Tufts College Medical School, a fellow of the American Medical Association and the American College of Physicians and a member of the Association of American Physicians, American Society for Clinical Investigation, American Clinical and Climatological Association, the Association for the Study of Internal Secretions, the American Association of Pathologists and Bacteriologists, and the American Society for Experimental Pathology.

He is survived by three daughters and a son.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR FEBRUARY, 1956

RÉSUMÉ

DISEASE	FEB. 1956	FEB. 1955	SEVEN-YEAR MEDIAN
Chancroid	9	4	3
Chicken pox	2465	2038	2044
Diphtheria	0	4	4
Dog bite	796	592	592
Dysentery, bacillary	0	9	6
Encephalitis, infectious	0	3	3
German measles	298	304	207
Gonorrhea	169	130	183
Granuloma inguinale	0	0	0
Hepatitis, infectious	29	124	21
Lymphogranuloma venereum	2	2	0
Malaria	0	0	0
Measles	570	13489	1332
Meningitis, meningococcal	5	2	5
Meningitis, Pfeiffer bacillus	5	3	4
Meningitis, pneumococcal	6	9	3
Meningitis, staphylococcal	1	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	4	6	5
Mumps	307	1562	1429
Poliomyelitis	5	2	1
Salmonellosis	41	19	8
Scarlet fever	787	768	628
Syphilis	169	147	147
Trichinosis	1	0	1
Tuberculosis, pulmonary	162	99	183
Tuberculosis, other forms	5	3	10
Typhoid fever	1	0	1
Undulant fever	3	1	1
Whooping cough	72	214	243

COMMENT

Diseases below the seven-year median were diphtheria, bacillary dysentery, measles, mumps and whooping cough.

For the first time since July, 1952, no cases of bacillary dysentery were reported.

During February, mumps was at its lowest level for this month since 1935.

Also during February, whooping cough was at its record low for this month in the history of the State.

Diseases above the seven-year median were chicken pox, German measles, infectious hepatitis, poliomyelitis, salmonellosis and scarlet fever.

Although infectious hepatitis was above the seven-year median, it was at its lowest level for this month since 1952.

Salmonellosis continues at a high level. It is accounted for by 1 or 2 cases in families rather than by any large outbreaks.

GEOGRAPHIC DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Anthrax: Lowell, 1.

Dysentery, amebic: Bedford, 1.

Hepatitis, infectious: Beverly, 1; Boston, 9; Cambridge, 1; Chelsea Naval Hospital, 1; Chicopee, 1; Fall River, 1; Gloucester, 1; Haverhill, 1; Lowell, 2; Ludlow, 1; Millbury, 1; Millis, 1; Scituate, 1; Sheffield, 1; Somerville, 2; Springfield, 1; Wareham, 1; Worcester, 2; total, 29.

Meningitis, meningococcal: Arlington, 1; Boston, 1; Lowell, 1; Lynn, 1; Provincetown, 1; total, 5.

Meningitis, Pfeiffer bacillus: Brockton, 1; Needham, 2; Quincy, 1; Watertown, 1; total, 5.

Meningitis, pneumococcal: Andover, 1; North Andover, 1; Peabody, 1; Saugus, 1; Worcester, 2; total, 6.

Meningitis, staphylococcal: Worcester, 1.

Meningitis, undetermined: Fall River, 1; Hingham, 1; Lawrence, 1; Taunton, 1; total, 4.

Poliomyelitis: Barnstable, 1; Braintree, 1; Cambridge, 1; Falmouth, 1; Southbridge, 1; total, 5.

Salmonellosis: Belmont, 1; Beverly, 1; Boston, 6; Brockton, 1; Brookline, 2; Danvers, 1; Dedham, 1; Fitchburg, 1; Framingham, 4; Greenfield, 3; Lexington, 1; Monson, 1; Newton, 5; Quincy, 1; Salem, 2; Somerville, 2; Spencer, 1; Waltham, 2; Wayland, 1; Westford, 1; Winthrop, 1; Worcester, 2; total, 41.

Trichinosis: Falmouth, 1.

Typhoid fever: Manchester, 1.

Undulant fever: Everett, 1; Gardner, 1; Watertown, 1; total, 3.

CORRESPONDENCE

A NOTE ON TRUSTEE-STAFF RELATIONS

To the Editor: The editorial and the letter of Dr. Charles H. Bradford on "Trustees and Hospitals," in the December 22, 1955, issue of the *Journal* were excellent. These have been discussed with other physicians and several lay groups, who agree unanimously that they should be given more attention and recognition.

Today, the hospital has become most important as the center of medical care for sick people. These patients are the ones who are affected by controversies between the trustees and the physicians. The consensus is that the role of the physicians on the medical staff is too important to the welfare of the patients to be harmed by this internal dissension in the hospitals.

Most trustees are public-spirited and co-operative persons with the interest of the patients, the staff physicians and the hospitals at heart, as are the majority of staff physicians. However, a few administrators and staff members of some hospitals are disloyal, self-seeking, ill adjusted and often misinformed.

If the leaders of the hospital staff are respected by the members as men of strength and integrity in their support, the trustees have never been known to attempt to use any authority to interfere with the functions of the staff. The same statement is true if all the members of the hospital staff and the director of the hospital are loyal to each other.

Too often trustees are indoctrinated with false information by some faithless, self-seeking staff member or director, causing discomfort and humiliation to the rest of the staff or to individual physicians.

In 1947 the Committee on Hospital and Professional Relations of the Massachusetts Medical Society met with a committee of the Massachusetts Hospital Association to attempt to settle differences of opinion between the doctors and the administration of hospitals. These committees were found inadequate to approach trustees.

In 1954 these same committees published a report providing a means by which both staff members and trustees may appeal to the Massachusetts Medical Society for settlement of any difficult problems. It is hoped that full co-operation by both trustees and staffs will bring about more amicable settlement of disputes in hospitals.

SIDNEY C. WIGGIN, M.D.

Boston

BOOK REVIEW

Clues in the Diagnosis and Treatment of Heart Disease. By Paul D. White, M.D. 8°, cloth, 186 pp., with 35 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $5.50.

The search for and recognition of clinical clues converts the workup of each patient into a potentially dramatic undertaking in which the art of medicine dominates the stage. The art derives from the faculty to grasp the essential, irrespective of how picayune, and to disregard the trivial, irrespective of how grandiose it may appear. Such a faculty represents a subtle and not always conscious interaction of sound experience and ample common sense. The author comes well equipped for the task he has undertaken. Not only does he draw on his own extensive practice but also he has gathered contributions from 90 other outstanding cardiologists hailing from nearly all parts of the world.

The book is divided into 13 short chapters and an appendix. The first 7 chapters are devoted to history taking and symptomatic aspects of cardiac illness. Objective findings, including clues derived from the electrocardiogram and chest roentgenogram, are dealt with in succeeding 5 chapters. The last chapter briefly appraises the clues to be gained from therapy. The book is clearly written and well organized and on the whole provides many valuable pointers and short-cuts to correct diagnosis. The most lucidly composed section is the one dealing with the patient's story. The importance of careful history taking is properly emphasized and adequately documented. The chapters on electrocardiography and roentgenology cursorily deal with the common abnormal patterns to be found in most textbooks on heart disease. This volume is excellently printed and illustrated. At a time when medical "pearls" are much valued, Dr. White's short treatise on clues in diagnosis and treatment of heart disease is a worth-while contribution.

BERNARD LOWN, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Dispensatory of the United States of America. By Arthur Osol, Ph.D., Ph.G., M.S., professor of chemistry and director, Department and School of Chemistry, Philadelphia College of Pharmacy and Science, and member of the Committee of Revision of the *United States Pharmacopoeia;* and George E. Farrar, Jr., M.D., medical director, Wyeth Laboratories, Incorporated, associate professor of medicine, Temple University School of Medicine and Hospital, and member of the Committee of Revision of the *United States Pharmacopoeia.* With Karl H. Beyer, Jr., Ph.D., M.D.; John H. Brown, V.M.D.; David K. Detweiler, V.M.D., M.S.; Robertson Pratt, Ph.D.; and Heber W. Youngken, Ph.M., Ph.D., Sc.D. 25th edition. 4°, cloth, 2139 pp. Philadelphia: J. B. Lippincott Company, 1955. $25.00. (Based on the fifteenth revision of the *United States Pharmacopoeia,* the tenth edition of the *National Formulary,* the *British Pharmacopoeia, 1953,* and the first edition of the *International Pharmacopoeia,* Vol. 1 and 2.)

Surgery of the Ambulatory Patient. By L. Kraeer Ferguson, M.D., professor of surgery, Graduate School of the University of Pennsylvania, professor of surgery, Woman's Medical College of Pennsylvania, and surgeon, Graduate Hospital of the University of Pennsylvania, Woman's Medical College Hospital, Philadelphia General Hospital and Doctors Hospital. With a section on Fractures by Louis Kaplan, M.D., senior attending surgeon, Albert Einstein Medical Center, Southern Division, clinical professor of surgery, Hahnemann Medical College, and in charge of the Fracture Division of the Surgical Outpatient Department, Hospital of the University of Pennsylvania. Third edition. 8°, cloth, 866 pp., with 664 illustrations. Philadelphia: J. B. Lippincott Company, 1955. $12.00.

Premature Infants: A manual for physicians. By Ethel C. Dunham, M.D., director, Division of Research in Child Development, United States Children's Bureau, and consultant in pediatrics, World Health Organization, Geneva, Switzerland. Second edition, completely revised and reset. 8°, cloth, 459 pp., with 41 illustrations and 76 tables. New York: Paul B. Hoeber, Incorporated, 1955. $8.00.

Mental Hygiene in Public Health. By Paul V. Lemkau, M.D., professor of public-health administration, Division of Mental Hygiene, School of Hygiene and Public Health, Johns Hopkins University. Second edition. 8°, cloth, 486 pp., with 10 illustrations. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $8.00.

Present-Day Psychology: An original survey of departments, branches, methods, and phases, including clinical and dynamic psychology. Edited by A. A. Roback, with the collaboration of forty experts in the various fields. 8°, cloth, 995 pp., with illustrations. New York: Philosophical Library, 1955. $12.00.

The National Formulary: National Formulary X. Prepared by the Committee on National Formulary under the supervision of the Council by authority of the American Pharmaceutical Association. Tenth edition. (Official from December 15, 1955.) 8°, cloth, 867 pp. Washington, D.C.: American Pharmaceutical Association, 1955. $9.00. (Distributed for the Association by J. B. Lippincott Company, Philadelphia.)

Basic Surgical Skills: A manual with appropriate exercises. By Robert Tauber, M.D., assistant professor of gynecology and obstetrics, Graduate School of Medicine, University of Pennsylvania, senior attending physician in obstetrics and gynecology, Albert Einstein Medical Center, and chief of gynecology, Kensington Hospital. 4°, cloth, 75 pp., with 51 illustrations. Philadelphia: W. B. Saunders Company, 1955. $3.75.

Office Procedures. By Paul Williamson, M.D. 4°, cloth, 412 pp., with illustrations. Philadelphia: W. B. Saunders Company, 1955. $12.50.

Cancer Cells. By E. V. Cowdry, director, Wernse Cancer Research Laboratory, Washington University, St. Louis. 4°, cloth, 677 pp., with 137 illustrations and 50 tables. Philadelphia: W. B. Saunders Company, 1955. $16.00.

Textbook of Endocrinology. Edited by Robert H. Williams, M.D., executive officer and professor of medicine, University of Washington Medical School. Second edition. 8°, cloth, 776 pp., with 175 illustrations and 56 tables. Philadelphia: W. B. Saunders Company, 1955. $13.00.

Suprapubic Prostatectomy: With primary closure of the bladder by an original method: Preparation, technique, and post-operative treatment. By Univ.-Prof. Dr. Theodor Hryntschak. Authorized translation by Noble S. R. Maluf, M.S., M.D., Ph.D., chief of urology, Surgical Service, Veterans Administration Hospital, Houston, Texas, and assistant professor of urology, Baylor University College of Medicine. 8°, cloth, 187 pp., with 35 illustrations and 5 tables. Springfield, Illinois: Charles C Thomas, 1955. $8.50.

Pädiatrischer Röntgenatlas: Eine Sammlung typischer Bilder. By Dr. M. A. Lassrich, Prof. Dr. R. Prévôt and Prof. Dr. K. H. Schäfer, Hamburg. 4°, cloth, 333 pp., with 700 illustrations. Stuttgart: Georg Thieme, 1955. DM 115.- $27.40. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Clinical Roentgenology: The lungs and the cardiovascular system emphasizing differential considerations. Vol. 3. By Alfred A. de Lorimier, M.D., radiologist, Saint Francis Memorial Hospital, San Francisco, consultant in radiology to the United States Army, at the Letterman Army Hospital, and consultant in radiation therapy to the United States Public Health Service at the United States Marine Hospital, San Francisco; Henry G. Moehring, M.D., radiologist, Duluth Clinic, Duluth, Minnesota; and John R. Hannan, M.D., radiologist, Cleveland, and radiologist, Lake County Memorial Hospital, Painesville, Ohio, associate professor of diagnostic roentgenology, Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, and staff, Department of Roentgenology, Cleveland Clinic Foundation. 4°, cloth, 508 pp., with illustrations and tables. Springfield, Illinois: Charles C Thomas, 1955. $20.50.

J.A.M.A. Clinical Abstracts of Diagnosis and Treatment. Edited by Noah D. Fabricant. 8°, cloth, 627 pp. New York: Intercontinental Medical Book Corporation with Grune and Stratton, Incorporated, 1955. $5.50. (Published with the Approval of the Board of Trustees, American Medical Association.)

Semi-Micro Organic Preparations. By J. H. Wilkinson, B.Sc., Ph.D., F.R.I.C. 12°, cloth, 94 pp., with 23 illustrations and frontispiece. Springfield, Illinois: Charles C Thomas, 1955. $2.00.

A Short History of Medicine. By Edwin H. Ackerknecht, M.D., professor of the history of medicine, University of Wisconsin Medical School. 8°, cloth, 258 pp., with 28 illustrations. New York: The Ronald Press Company, 1955. $4.50.

The Quantitative Analysis of Drugs. By D. C. Garratt, B.Sc., Ph.D. (Lond.), F.R.I.C., chief analyst, Boots Pure Drug Company, Limited. Second edition, revised and enlarged. 8°, cloth, 670 pp., with 6 illustrations and 45 tables. New York: The Philosophical Library, 1955. $17.50.

Dextran: Its properties and use in medicine. By John R. Squire, M.D., F.R.C.P., Leith Professor of Experimental Pathology and director, Division of Pathological Studies, University of Birmingham; J. P. Bull, M.D., director, Medical Research Council Industrial Injuries and Burns Research Unit, Birmingham Accident Hospital, and University Research Fellow, University of Birmingham; W.d'A. Maycock, M.D., Lister Institute of Preventive Medicine, Elstree; and C. R. Ricketts, Ph.D., F.R.I.C., member, Scientific Staff, Medical Research Council, and University Research Fellow, University of Birmingham. 8°, cloth, 91 pp., with 7 illustrations and 5 tables. Springfield, Illinois: Charles C Thomas, 1955. $3.00.

The Restricted Sodium Diet: Compiled under the supervision of the Diets and Dietary Products Committee of the Los Angeles County Heart Association. Edited by Elizabeth Reisinger. 8°, paper, 64 pp. Los Angeles: Los Angeles County Heart Association, 1955.

Modern Medicine Annual 1956: An annual publication containing the articles that appeared in the twenty-four issues of Modern Medicine *during 1955. Part One. January 1 through June 15.* 8°, cloth, 920 pp., with illustrations and tables. Minneapolis: Modern Medicine, 1955.

Wiederbelebung. By Prof. Dr. H. Killian, Freiburg/Br.; and Priv.- Doz. Dr. A. Dönhardt, Hamburg. 8°, cloth, 320 pp., with 93 illustrations. Stuttgart: Georg Thieme, 1955. $5.70. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Polycythemia: Physiology, diagnosis and treatment based on 303 cases. By John H. Lawrence, M.D., D.Sc., director, Donner Laboratory, professor of medical physics and physician-in-chief, Donner Pavilion, University of California. 8°, cloth, 136 pp., with 38 illustrations and 8 tables. New York: Grune and Stratton, Incorporated, 1955. $5.50. *(Modern Medical Monographs.)*

High Blood Pressure. By George White Pickering, M.A., M.B. (Cantab.), M.D. (Ghent), F.R.C.P., physician to St. Mary's Hospital and professor of medicine, University of London. 8°, cloth, 547 pp., with 106 illustrations, 5 in color, and 23 tables. New York: Grune and Stratton, 1955. $9.50.

Human Pathology. By Howard T. Karsner, M.D., LL.D., medical research advisor to the Surgeon General of the United States Navy. Eighth edition. 4°, cloth, 960 pp., with 557 illustrations and 14 colored plates. Philadelphia: J. B. Lippincott Company, 1955. $15.00.

Quarterly Cumulative Index Medicus. Vol. 53. January-June, 1953. Prepared in the Library under the Supervision of Austin Smith, M.D., editor, *Journal of the American Medical Association,* and Magdalene Freyder, librarian. 4°, cloth, 1775 pp. Chicago: American Medical Association, 1955. Subscription price: $20.00 per year.

Introduction to Operating-Room Technique. By Edna Cornelia Berry, R.N., head nurse, Operating Rooms, University Hospitals of Cleveland; and Mary Louise Kohn, R.N., M.N. 4°, paper, 154 pp., with illustrations. New York: The Blakiston Division, McGraw-Hill Book Company, Incorporated, 1955. $4.00.

NONCLINICAL NOTES

DR. MURRAY SNELL DANFORTH FUND

Dr. Murray S. Danforth, one of New England's outstanding orthopedic surgeons before his death in 1943, has been memorialized by his sister, the late Miss Agnes H. Danforth, of Bangor, Maine. Miss Danforth left a bequest of $10,000 in her will for the purpose of establishing the Dr. Murray Snell Danforth Fund, the income from which will be used to award scholarships for Maine residents preparing for the medical or related professions at Bowdoin College.

NOTICES

COUNCIL OF THE NEW ENGLAND MEDICAL SOCIETIES

The eleventh annual meeting of the Council of the New England Medical Societies will be held at the Hotel Statler, Boston, on Wednesday, April 11, at 4:30 p.m. The subject for the meeting will be "Hospital and Professional Relations." Heading the discussion will be Dr. Jacob H. Fine

and a hospital trustee, to be announced. Physicians wishing to attend should get in touch with Mr. Everett R. Spencer, secretary-treasurer, 22 Fenway, Boston 15, Massachusetts.

SOLDIERS HOME, CHELSEA

A professional-staff meeting of the Soldiers Home, Chelsea, will be held in the auditorium of the Quigley Memorial Hospital on Wednesday, April 25, at 7:15 p.m. Dr. Howard Frank will give a talk entitled "The Present Status of Surgical Treatment of Coronary Artery Disease." All physicians are invited.

SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the Lemuel Shattuck Hospital, 170 Morton Street, Jamaica Plain, on Tuesday, April 17, at 12 noon. The program will be presented by the medical staff.

All physicians are invited to attend.

THIRD ANNUAL SURGICAL SEMINAR

The third annual surgical seminar of the Third (Boston University) Surgical Service of the Boston City Hospital will be held in the Dowling Amphitheater, Boston City Hospital, on Wednesday, April 18. The seminar will be on the subject, "Modern Developments in Surgery." Dr. Eugene E. O'Neil will be chairman. The program is as follows:

10:00 a.m. Portal Decompression for Portal Hypertension. Charles G. Child, III, M.D.
10:30 a.m. Gastrointestinal Hemorrhage. George F. Miller, M.D.
11:30 a.m. A New Concept of Wound Healing. J. Englebert Dunphy, M.D.
12:00 m. Total Gastrectomy with Roux-en-Y Esophagojejunostomy in the Treatment of Gastric Cancer. H. William Scott, Jr., M.D.
2:00 p.m. Unusual Problems in Gall-bladder Surgery. Robert J. Coffey, M.D.
2:30 p.m. The Pathologic Process in Pancreatitis. Henry Doubilet, M.D.
3:30 p.m. A Report from the Third (B. U.) Surgical Research Laboratory. John J. Byrne, M.D.
4:00 p.m. Ulcerative Colitis and Regional Ileitis. Bentley P. Colcock, M.D.

All physicians are invited to attend.

MASSACHUSETTS CHAPTER, AMERICAN ACADEMY OF GENERAL PRACTICE

The semiannual scientific meeting of the Massachusetts Chapter of the American Academy of General Practice will be held at the Hotel Statler, Boston, on Sunday, April 22. The program is as follows:

Opening Address. Office Gynecology. Dr. Robert Greenblatt, Augusta, Georgia.
Practical Demonstration of Fracture Treatment. Dr. Edward Compere, Chicago, Illinois.
Office Proctology. Dr. Louis A. Buie, Rochester, Minnesota.
Recent Advances in the Treatment of Skin Eruptions. Dr. Arthur Curtis, Ann Arbor, Michigan.
Childhood Immunization with Specific Reference to Poliomyelitis. Dr. Harriet M. Felton, Galveston, Texas.
The Use of Radioactive Isotopes in Diagnosis and Treatment. Dr. Eugene L. Saenger, Cincinnati, Ohio.

The guest speaker will be Dr. William Hildebrand, of Menasha, Wisconsin, formerly, national president of the Academy.

SOCIETY MEETINGS AND CONFERENCES

April 5. Second Annual Symposium on Cardiovascular Disease. Page 490, issue of March 8.
April 6. Massachusetts Society of Anesthesiologists. Page 539, issue of March 15.
April 6–7. New York Academy of Sciences. Page 628, issue of March 29.
April 7. American Congress of Physical Medicine and Rehabilitation. Page 491, issue of March 8.
April 8. American College of Gastroenterology. Page 491, issue of March 8.
April 10. Harvard Medical Society. Page 628, issue of March 29.
April 11. Council of the New England Medical Societies. Page 675.
April 12. Nu Sigma Nu Fraternity. Page 491, issue of March 8.
April 15–20. American College of Allergists. Page 399, issue of February 23.
April 16. Hartford Medical Society. Page 242, issue of February 2.
April 16–18. Aero Medical Association. Page 585, issue of March 22.
April 16–21. American Academy of Pediatrics. Page 399, issue of February 23.
April 17. South End Medical Club. Notice above.
April 18. Greater Boston Medical Society. Page 208, issue of August 4.
April 18. Third Annual Surgical Seminar. Notice above.
April 22. Massachusetts Chapter, American Academy of General Practice. Notice above.
April 23–26. International Academy of Proctology. Page 399, issue of February 23.
April 25. Soldiers Home, Chelsea. Notice above.
April 25. Massachusetts Heart Association. Page 490, issue of March 8.
April 26. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.
May 1–5. Sixth National Congress on Pediatrics. Page 491, issue of March 8.
May 2. Postgraduate Medical Institute. Page 487, issue of September 15.
May 3–5. American Goiter Association. Page 348, issue of August 25.
May 14–18. American Nurses' Association. Page 491, issue of March 8.
May 22–24. Massachusetts Medical Society Annual Meeting.
May 28–June 1. European Symposium on Vitamin B. Page 578, issue of September 29.
June 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.
June 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.
June 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.
June 21–24. American Academy of Dental Medicine. Page 944, issue of December 1.
August 19–23. American College of Chest Physicians. Page 840, issue of November 10.
September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
September 10–14. American Dietetic Association. Page 1180, issue of December 29.

Calendar for the Week Beginning Thursday, April 12

Thursday, April 12
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Staff Conference. The Adrenal Androgens. Dr. Paul L. Munson. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Effect of High Humidity Upon the Respiratory Tract. Dr. Roe E. Wells. Main Amphitheater, Peter Bent Brigham Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

Friday, April 13
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

(Continued on page xxviii)